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British Journal of Anaesthesia

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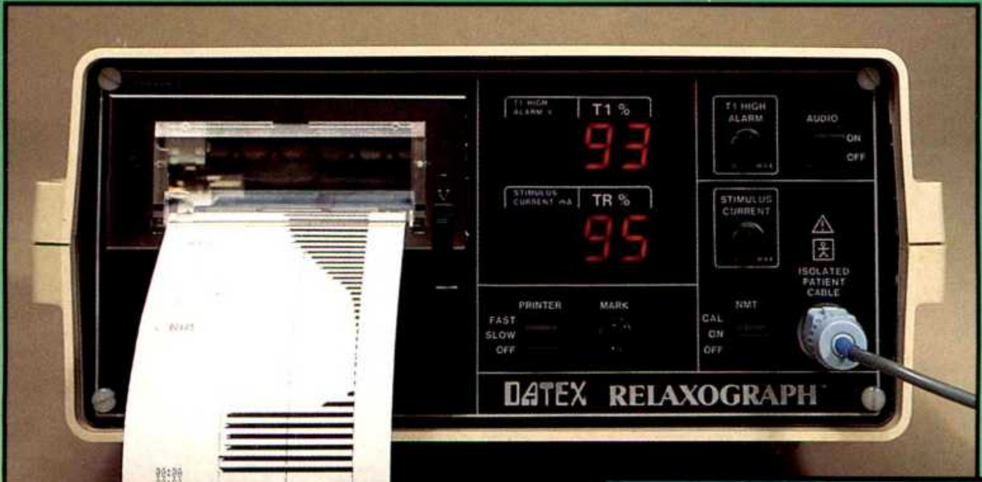

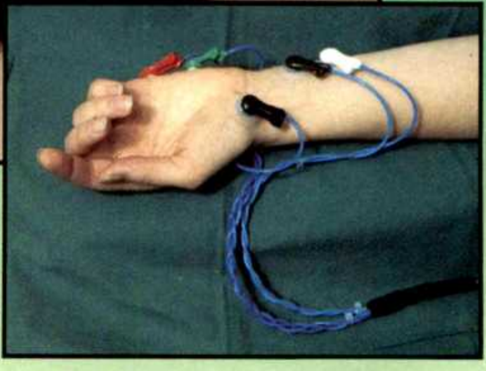

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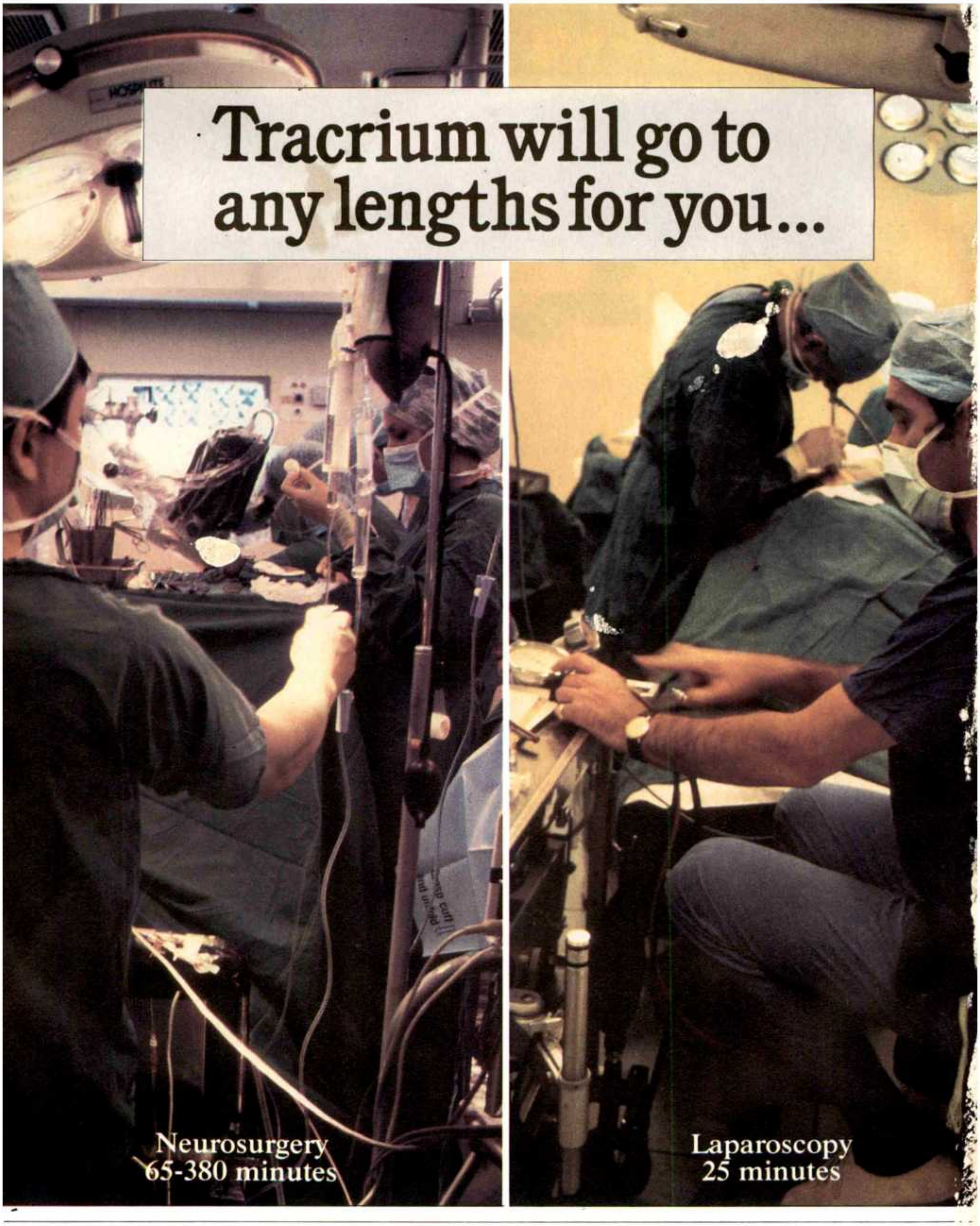

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Contra-indications, warnings, etc. Contra-indicated in patients hypersensitive to atracurium besylate. Tracrium should be used with caution in patients receiving aminoglycosides or polypeptide antibiotics and in patients with myasthenia gravis. In common with all other neuromuscular blocking agents, adequate facilities must be available for endotracheal intubation and artificial ventilation. The neuromuscular block produced by Tracrium may be increased by the concomitant use of inhalational anaesthetics such as halothane. Tracrium should not be mixed in the same syringe with any other agent; in particular it must not be mixed with thiopentone or any alkaline agent, as the high pH would cause inactivation of the Tracrium. As with all other neuromuscular blocking agents the possibility of transient hypotension due to histamine release cannot be excluded. Although animal studies have indicated that Tracrium has no adverse effects on foetal development, nevertheless, like all neuromuscular blocking agents, it should be used with caution in pregnant women. Tracrium may be used to maintain neuromuscular relaxation in Caesarean section as atracurium does not cross the placenta in clinically significant amounts.

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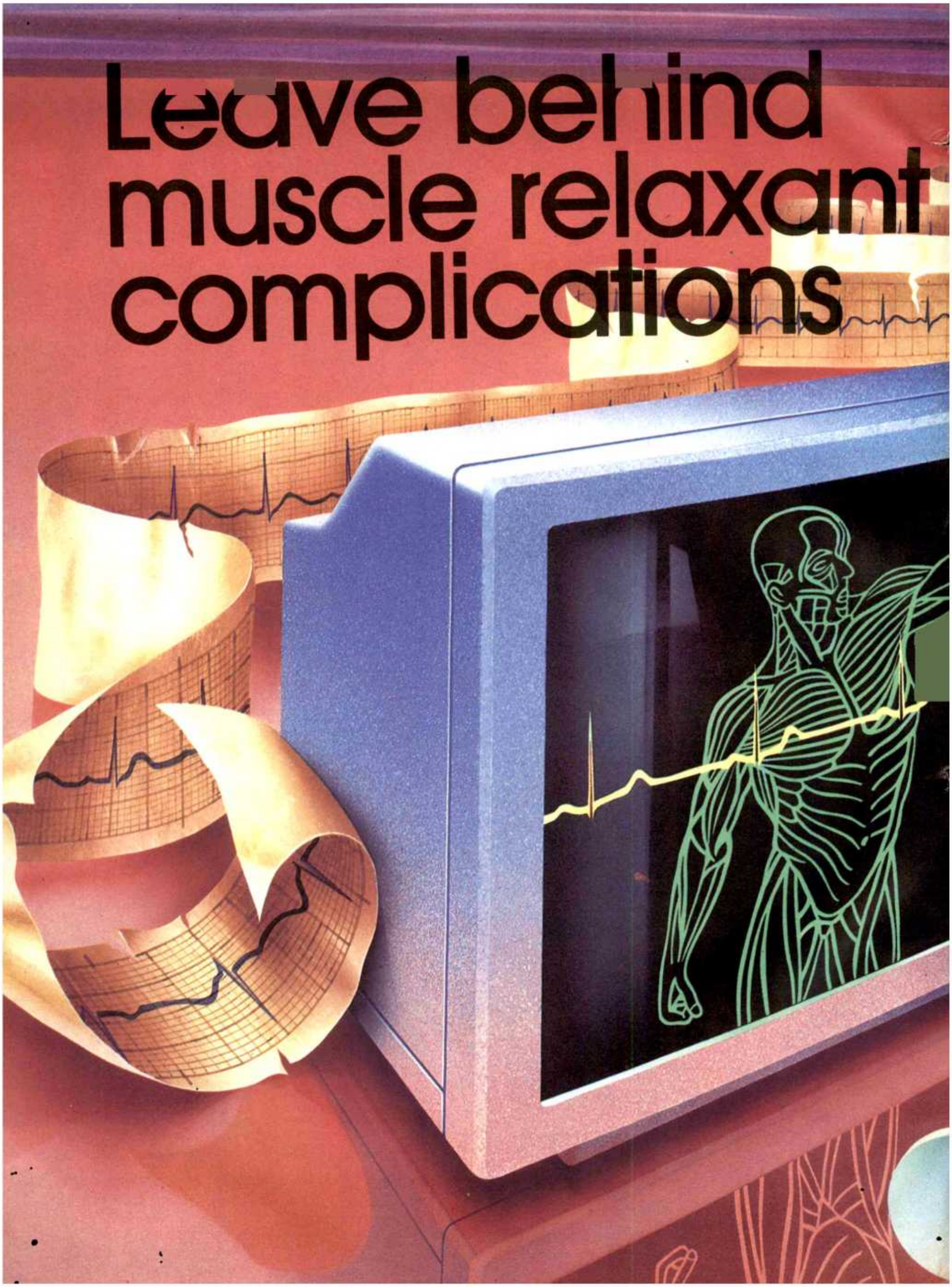
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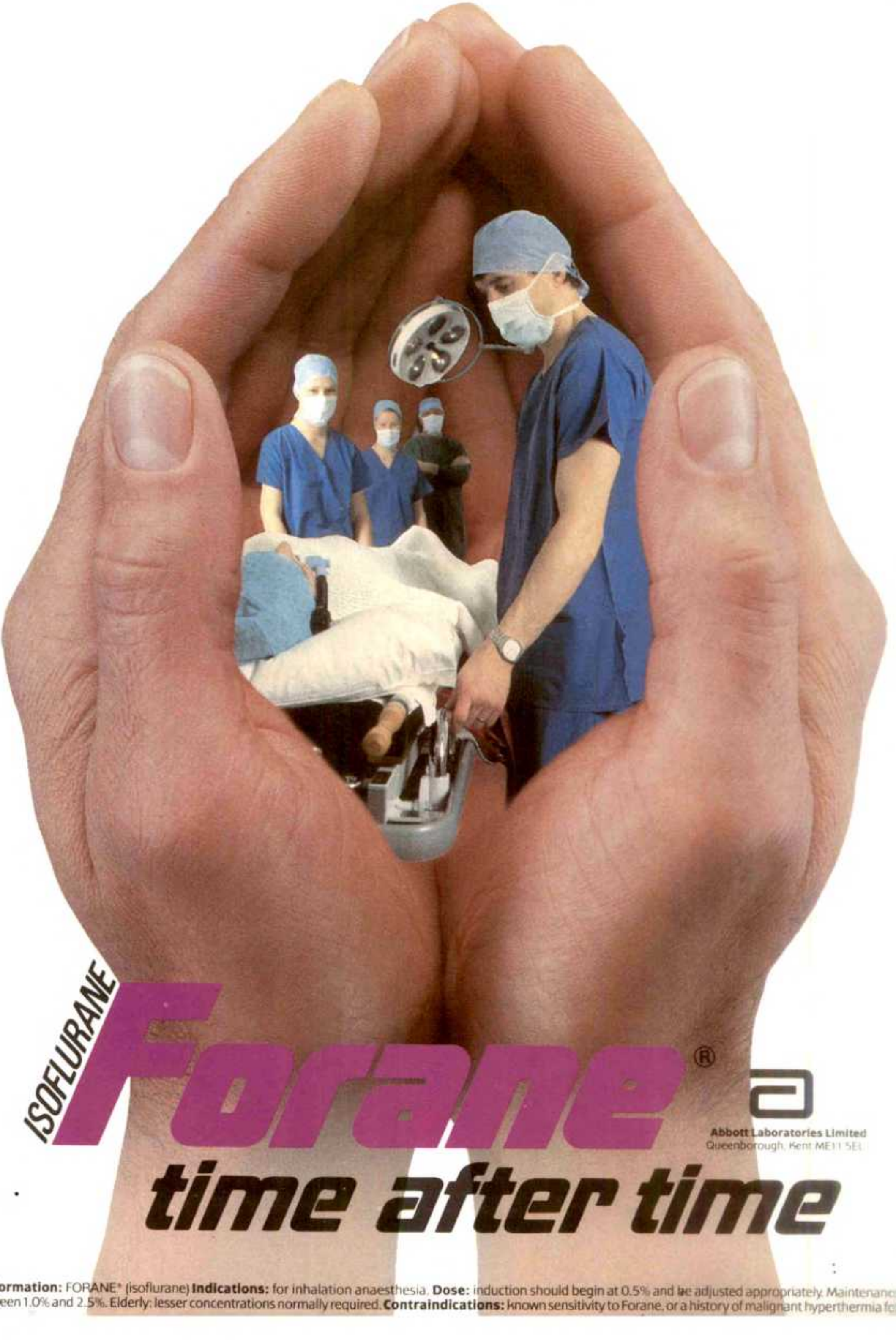

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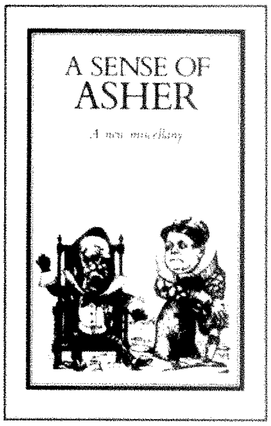

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BRITISH JOURNAL OF ANAESTHESIA

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EDITORIAL

ADVERSE EFFECTS OF DRUGS USED IN ANAESTHESIA

These postgraduate educational issues of the *British Journal of Anaesthesia* are intended to provide an authoritative and current review of selected topics of interest in anaesthesia and related disciplines. It is self-evident that the factual knowledge of adverse effects is of direct benefit to patient safety, but the fundamental concepts, which are so much more important for good clinical practice, are surprisingly complex. An overview of the subject needs to distinguish between at least four general categories: overdose effects, side actions, abnormal responses and drug interactions. An overdose can be either relative or absolute, but an important factor is the spread of sensitivity to the drug effect within the general population. This finite variability of response is relevant to the degree of predictability of an overdose effect. Side actions are usually more predictable than overdose effects as they accompany the major drug action and are only called side actions because the physician attempts either to minimize or to ignore their effects. It is, of course, only a proportion of these actions which need to be classified as adverse. In contrast to these first two categories, abnormal responses are characterized by their unpredictability and the rarity of the events. Finally, drug interactions have to come into a separate category because not only do they modulate separate drug actions, but also they can introduce hitherto new and unsuspected adverse effects.

In planning this postgraduate issue, the complexity of the subject was recognized and it was decided to group the adverse effects by considering those associated with principal drug groups, rather than combining the actions of different types of drugs on specific organ systems. In order to avoid the danger of the subdivisions degenerating into a catalogue of contraindications—which would duplicate material already published—the guest contributors were asked to consider the different drug effects in terms of both underlying principles and clinical relevance.

The true overall incidence of anaesthetic morbidity is unknown, but all would accept that anaesthetic drugs can be associated with iatrogenic injury if administered at high enough concentrations. This aspect of the problem is not necessarily synonymous with an overdose effect. For example, the adverse actions of local anaesthetics have been considered in terms of local and focal effects—both of which are associated with high concentrations of the agents—in contrast to systemic effects which are produced at low concentrations following absorption into the general circulation. One of the complications of adverse effects is that what is considered an acceptable physiological response in one set of circumstances becomes an adverse effect in another. This is the case with the respiratory depression associated with the opioids. During operation, far greater degrees of respiratory depression are compensated for by artificial ventilation, but it is the fact that these drugs continue to have subtle effects, or are administered during the postoperative period, that gives rise to the concern about adverse effects.

The distinctive feature of many of the drugs used in anaesthesia is the lack of specificity in their actions. One generalization is that a drug with non-specific multiple actions is more likely to have associated adverse effects. This is not, of course, true of all drugs, and the review of the neuromuscular blocking drugs concentrates on more specific adverse effects. Anaesthesia may involve polypharmacy, with many drugs being used as part of the anaesthetic regimen. For this reason a review of drug interactions seemed appropriate, since a knowledge of this subject must form an increasing part of the essential information for the modern anaesthetist.

Research on the adverse effects of general anaesthetics is proceeding intensively both in the laboratory and in the clinical field. Advances in these two areas do not necessarily go hand in hand. For example, in the case of nitrous oxide, there is a mass of biochemical data, but an absence of obvious adverse clinical effects. This apparent contradiction can only be resolved by more clinical studies. On the other hand, the paper on the volatile agents brings out the opposite problem. The clinical evidence for and against anaesthetic-associated hepatitis has accumulated for many years, but we will be unlikely to be able to specify the predisposing factors more precisely until there have been advances in our understanding of the underlying biotransformation and immunological mechanisms.

Adverse effects of drugs is a topic which unites the theoretical, experimental and practical interests of anaesthetists. This is especially true in the case of the new i.v. agents; further clinical evaluation will be required for the recently released agents, particularly when they are administered by continuous infusions for prolonged sedation in intensive therapy units over periods of weeks. It is necessary to know the methods of investigation of allergic and hypersensitivity reactions in order to take up the challenge of learning more about these aspects of the drugs. Finally, the medical profession must be one of the few groups who have co-operated with such success in a prospective study of the potential adverse effects of anaesthetic environmental pollution. Some 11 000 woman have been recruited into the anaesthetists' 5-year epidemiological study which finished at the end of 1986. For these reasons this seems a particularly opportune time to review all the adverse effects of drugs used in anaesthesia.

What is needed in the future is for everyone to improve their reporting of the adverse effects of all drugs. In Britain the reporting system includes the use of a yellow card on which the details of all apparent reactions are notified to the Committee on Safety of Medicines. A possible modification, currently being considered, is the introduction of what has been called "the red card" specifically for acute adverse reactions. Such a system could be particularly relevant to anaesthetists, whose potential problems are somewhat different from those of other physicians.

M. J. Halsey

Br. J. Anaesth. (1987), 59, 3–13 001P01-37

CLINICAL ASPECTS OF THE INTERACTION BETWEEN NITROUS OXIDE AND VITAMIN B_{12}

J. F. NUNN

Vitamin B_{12} is a bound coenzyme of methionine synthase and has a tetrapyrrole ring with monovalent cobalt at the centre. The cobalt functions as a methyl carrier in the transmethylation reaction shown in figure 1. In 1968, Banks, Henderson and Pratt reported that nitrous oxide reacted *in vitro* with vitamin B_{12}, converting the cobalt from the monovalent form (Cob(I)alamin) to the bivalent form (Cob(II)alamin), which can no longer function as a methyl carrier. Their paper, in a journal not perused by many in the biomedical field, remained unnoticed by both haematologists and anaesthetists for 10 years.

In a seminal study, Amess and his colleagues (1978) showed that 24 h of administration of nitrous oxide to patients caused interference with deoxyribonucleic acid (DNA) synthesis, and they correctly inferred that nitrous oxide had interfered with the function of vitamin B_{12}. A few months later, Deacon and her colleagues (1978) showed that nitrous oxide did in fact cause rapid inhibition of the activity of methionine synthase in the rat.

Also in the same journal and the same year, Layzer (1978) reported a condition resembling sub-acute combined degeneration of the cord in 15 patients who had been chronically exposed to high concentrations of nitrous oxide. There was thus a parallel with megaloblastic anaemia and a working hypothesis for the agranulocytosis and the teratogenesis which had previously been observed as toxic effects of nitrous oxide.

Metabolic changes

So far as is known, nitrous oxide interacts in the body only with vitamin B_{12}. This is the coenzyme for both methionine synthase and methylmalonyl CoA mutase. Vitamin B_{12} does not function as a methyl carrier in the latter enzyme, which is not directly affected by nitrous oxide. Methionine synthase activity is, however, rapidly inhibited in mouse, rat and (more slowly) in man. Recovery is slow and, in the rat, takes several days, probably requiring the synthesis of new apoenzyme and absorption of new unoxidized vitamin B_{12}. This is because the oxidation is irreversible and, furthermore, the inactivated B_{12} is thought to be irreversibly bound to the apoenzyme.

In the present state of knowledge, it appears that the sole biochemical effect of nitrous oxide is to block the transmethylation reaction shown in figure 1. However, the metabolic consequences are not trivial. There are two products of the reaction, methionine and tetrahydrofolate. Metabolic consequences may be attributable to depletion of either or both products. However, their relative importance is not yet clarified, particularly in the clinical situation where other biochemical abnormalities may be present.

Methionine and its metabolites (fig. 2). Methionine is a dietary constituent, but its daily turnover is approximately double the dietary intake. Therefore, methionine is recycled from homocysteine, via S-adenosyl methionine and S-adenosyl homocysteine (fig. 3). Two pathways are available to methylate homocysteine. The first is catalysed by methionine synthase (fig. 1) and is affected by nitrous oxide. The second is the betaine pathway which is shown in figure 3. It is not affected by nitrous oxide, but is induced in the rat liver when the methionine synthase pathway is blocked by nitrous oxide (Lumb et al., 1983).

Catabolism and protein synthesis are normally in balance, but not when patients are catabolic. Conventional parenteral nutrition can easily supply the daily requirement of methionine. In addition to its role in protein synthesis, methionine is important as the precursor of S-adenosyl methionine, which is the direct methyl-group

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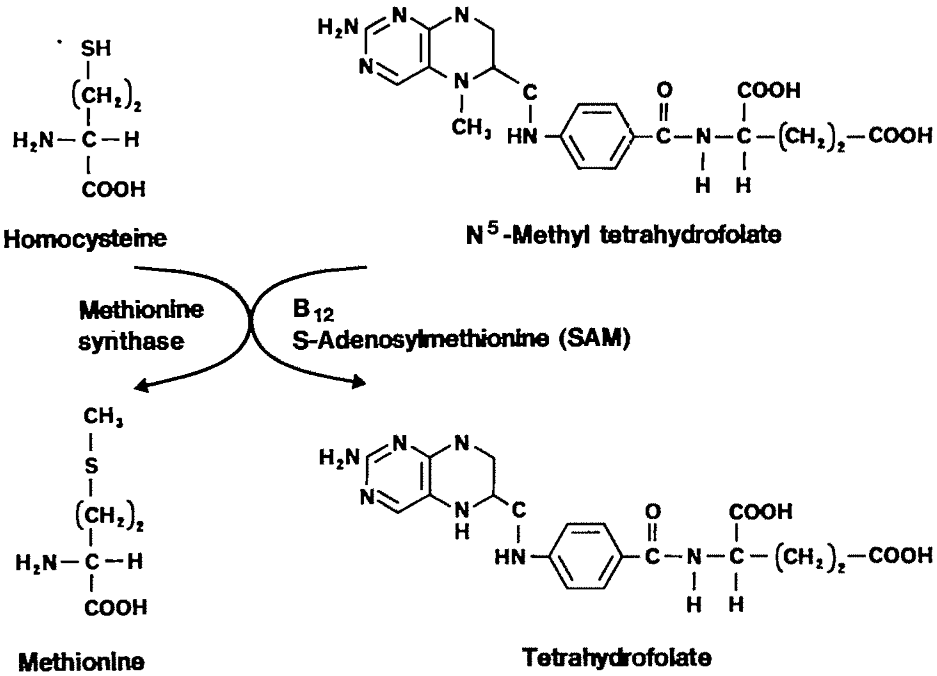

FIG. 1. The transmethylation reaction in which vitamin B_{12} is a co-factor for the enzyme methionine synthase.

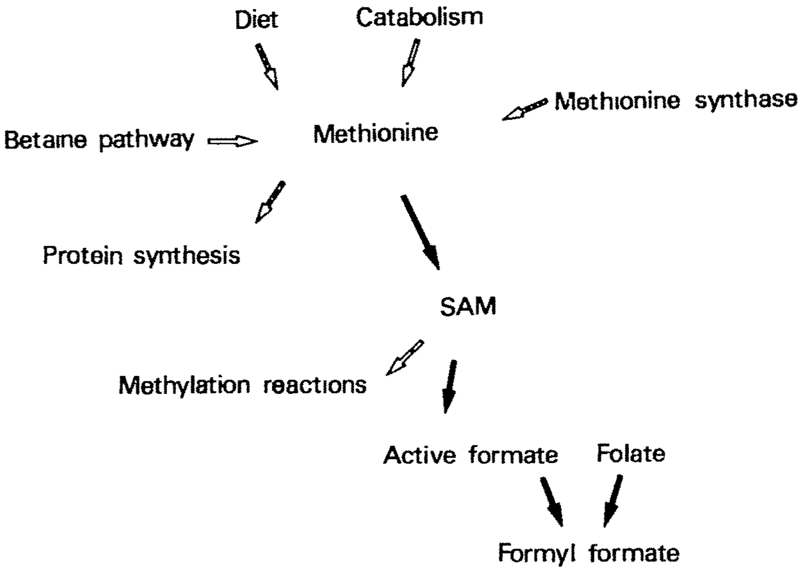

FIG. 2. Factors influencing the balance of methionine and S-adenosyl methionine (SAM).

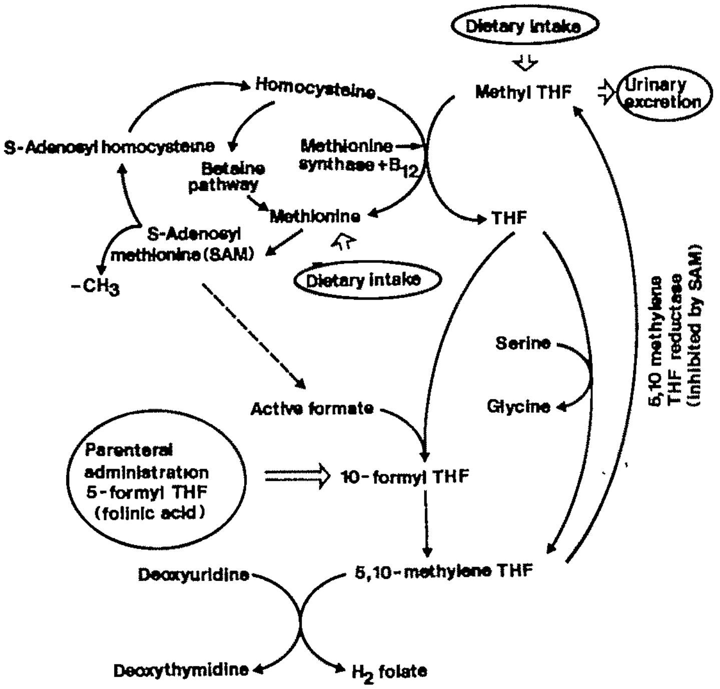

FIG. 3. Simplified metabolic pathway to show the relationship between the methionine synthase reaction and the synthesis of deoxythymidine. THF = tetrahydrofolate.

donor for a large number of methylation reactions including, for example, the conversion of noradrenaline to adrenaline, and the synthesis of arachidonic acid. Methylation is also concerned in myelination, and sub-acute combined degeneration of the cord probably results from depletion of S-adenosyl methionine. Of special importance is the production of active formate which reacts with tetrahydrofolate to yield formyl tetrahydrofolate (fig. 3).

In spite of the undoubted effect of nitrous oxide on methionine synthase, there is no measurable change in plasma methionine or S-adenosyl methionine concentrations in man during the first 3 h of anaesthesia with nitrous oxide (Nunn, Sharer et al., 1986), but concentrations of plasma methionine were decreased to 15–25% of the preoperative values between 8 and 24 h of administration of nitrous oxide (Skacel et al., 1983). However, less profound reductions were also observed in two control patients anaesthetized for 24 h with etomidate but no nitrous oxide. These patients reached minimal values of methionine concentration after 12 h of anaesthesia, but the methionine concentration returned to the preoperative value before the end of the 24 h of etomidate anaesthesia. Nunn, Sharer and colleagues (1986) confirmed earlier observations that routine preoperative starvation reduces the concentration of amino acids in plasma by about 30%. However, S-adenosyl methionine concentrations were unchanged either by preoperative starvation or by 3 h of nitrous oxide anaesthesia.

Two groups have reported on changes in methionine and S-adenosyl methionine concentrations following prolonged exposure of the rat to 50–70% nitrous oxide (Lumb et al., 1983; Viña, Davis and Hawkins, 1986). Results for 24 h exposure are summarized in table I. There is a consistent finding of a reduction in both methionine and S-adenosyl methionine in both studies, although results do not always attain statistical significance. Food was withheld in Viña's study but was available *ad libitum* in Lumb's study. There is, however, good evidence that exposure of the rat to nitrous oxide for shorter durations causes significant reductions in the hepatic concentrations of S-adenosyl methionine. Makar and Tephly (1983) reported an approximately 50% reduction in the hepatic concentration of

TABLE I. *Changes in methionine and S-adenosyl methionine (SAM) concentrations following 24 h exposure of rats to 50–70% nitrous oxide.* † *Lumb and colleagues (1983): 50% nitrous oxide; numbers too small for statistical analysis.* ‡ *Viña, Davis and Hawkins (1986): 70% nitrous oxide*

	Control	Nitrous oxide	P
Plasma			
Methionine (nmol ml^{-1})			
Lumb†	38	24	
Viña‡	84	69	ns
Liver			
Methionine (nmol g^{-1})			
Lumb†	112	94	
Viña‡	177	98	< 0.05
SAM (nmol g^{-1})			
Lumb†	99	91	
Viña‡	70	53	ns
Brain			
Methionine (nmol g^{-1})			
Lumb†	37	22	
Viña‡	54	29	< 0.05
SAM (nmol g^{-1})			
Lumb†	30.5	28	
Viña‡	23	15	< 0.05

S-adenosyl methionine after 2 h exposure to nitrous oxide and Ells and colleagues (1982) observed a 33% reduction after 4 h.

Folates (fig. 3). Deoxythymidine, an essential base in DNA, is synthesized from deoxyuridine and the obligatory carbon donor for this reaction is 5,10-methylene tetrahydrofolate (THF). This is formed by the serine pathway from THF, but in man the more important pathway is from methenyl THF, which is in turn derived from 10-formyl THF. The sequence of events in administration of nitrous oxide in both man and rat is as follows. The first detectable change is interference with the methionine synthase reaction. Shortly afterwards, there is interference with DNA synthesis, manifest by an abnormal deoxyuridine supression test. This is presumably attributable to depletion of formyl folate resulting from depletion of one or other or both of the products of the transmethylation reactions.

The pattern of depletion of folate compounds during exposure to nitrous oxide is not fully clarified. Total folate concentrations in liver of rats were found to decrease to approximately one-half of control values during 48 h exposure to 50% nitrous oxide (Lumb et al., 1980). During the first 24 h, most of the decrease is attributable to non-methylated folate, indicating trapping in the form of methyl THF, as a result of block of the transmethylation reaction. However, there appears to be escape from the folate trap during succeeding days of exposure to nitrous oxide. In contrast to hepatic folate, serum folate increases during exposure to nitrous oxide in man (Skacel et al., 1983). This indicates interference with entry of folate to the cells which requires conversion to folate polyglutamate, the normal intracellular form of all folates.

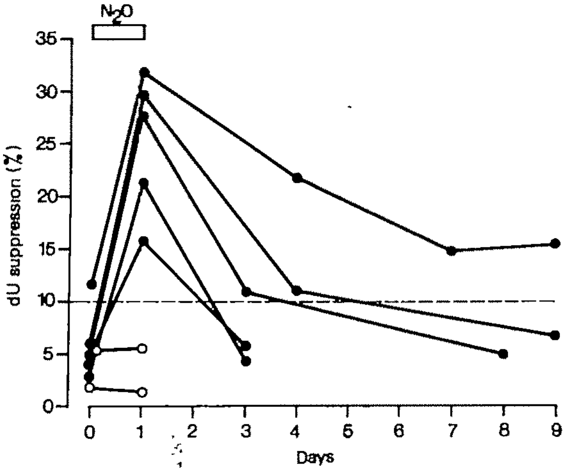

FIG. 4. Time course of changes in deoxyuridine suppression test in patients exposed to nitrous oxide for 24 h (●). Control patients received etomidate instead of nitrous oxide (○). Values over 10% are abnormal in our laboratory. Reproduced with permission from Skacel and colleagues (1983).

Interference with DNA synthesis is responsible for the megaloblastic changes and agranulocytosis which follow prolonged administration of nitrous oxide in man, but not in experimental animals. It is probably also the main cause of the fetotoxicity attributable to nitrous oxide.

Haematological changes

Megaloblastic changes in bone marrow are consistently found in patients who have been exposed to anaesthetic concentrations of nitrous oxide for 24 h (Amess et al., 1978; Skacel et al., 1983). This is associated with abnormal values for the deoxyuridine suppression which are comparable to those found in pernicious anaemia. It is a consistent finding that exposures to nitrous oxide lasting 4 days or longer result in agranulocytosis (Ablett, 1956; Lassen et al., 1956; Wilson, Martin and Last, 1956). For exposures lasting 24 h, stores of mature polymorphs in the peripheral blood are normally sufficient to prevent a reduction in the number of granulocytes in the peripheral blood during the interval before recovery of DNA synthesis (fig. 4). However, in two of seven patients who received nitrous oxide for 24–36 h (Skacel et al., 1983) the neutrophil count decreased by the 2nd to 4th days to 1×10^9 litre^{-1}. There was also an increased proportion of hypersegmented polymorphs in the circulating blood from the 4th to 14th days after operation.

The effect of exposures lasting less than 24 h is not fully clarified and is considered below. There is now considerable evidence that the abnormal deoxyuridine suppression test and the megaloblastic changes can be reversed by treatment with 5-formyl THF (folinic acid) which is converted in the body to 10-formyl THF. This is further considered below.

Teratogenesis

As expected, nitrous oxide crosses the placenta, and it has been shown in rats that fetal methionine synthase activity is inhibited soon after the effect is demonstrable in the maternal liver (Baden, Serra and Mazze, 1984). Fink, Shepard and Blandau (1967) exposed Sprague–Dawley rats to nitrous oxide for 2 days at the period of maximal organogenesis and observed a highly significant increase in skeletal deformities. Lane and colleagues (1980) extended these observations and showed an increased incidence of resorption and abnormalities (including skeletal) in the same species exposed to 70% nitrous oxide on the 9th day of pregnancy. Xenon had no effect and this convincingly showed it to be specific to nitrous oxide and not a general effect of anaesthesia *per se*. Keeling and colleagues (1986) confirmed Lane's findings and also demonstrated that the effect could, to a large extent, be reversed by pretreatment with folinic acid. This confirmed the view that the fetotoxicity of nitrous oxide was, in fact, the result of depletion of folates, and also suggested a feasible method of avoiding the effect. Pope and colleagues (1978) exposed pregnant rats of the same species to 50% nitrous oxide throughout pregnancy without observing any changes in the offspring other than decreased fetal weight. The betaine pathway of methionine synthesis would have been induced in the first few days of exposure (Lumb et al., 1983).

Extrapolation of data from rats to man is fraught with difficulty. Apart from species differences considered below, the circumstances of exposure of pregnant women to nitrous oxide are different from the pattern adopted in laboratory exposure of rats. The commonest anaesthetics administered in pregnancy are for relatively short procedures and at the end of the major period of organogenesis. Whatever the explanation, there are now a large number of epidemiological studies which are unanimous in finding no increased incidence of fetal malformations following the administration of anaesthetics in pregnancy (Smith, 1963; Snider and Webster, 1965; Brodsky et al., 1980; Duncan et al., 1986; Konieczko, Chapple and Nunn, 1987).

Time course of inhibition of methionine synthase and DNA synthesis

Methionine synthase activity. Investigation of the major biochemical effects of nitrous oxide require sampling of tissue (liver, bone marrow and brain) and it is understandable that most of the work has been undertaken in experimental animals, particularly rodents. Nevertheless, it is becoming apparent that there are important species differences between rat and man in the time course of inhibition.

In rodents, inhibition of methionine synthase is more than 50% in less than 30 min of exposure to nitrous oxide (Deacon et al., 1978; Koblin et al., 1981). Studies in progress by Minty with the author (unpublished) have shown that, in fact, methionine synthase activity is reduced to less than 50% after only 5 min exposure of Sprague–Dawley rats to 50% nitrous oxide.

The time course is very different in man. In a series of seven liver biopsies reported by Koblin and colleagues (1982), inhibition averaged 50% after about 2 h exposure to a mean concentration of 60% nitrous oxide. An even slower onset of inhibition of methionine synthase activity of bone marrow in patients anaesthetized with nitrous oxide was reported by Kano and colleagues (1981). Current studies by the author and Minty (unpublished) fully confirm that inhibition is slower in man than in rodents by an order of magnitude, although there is considerable individual variation in individual residual methionine synthase activity after various periods of exposure. They have found some patients with negligible activity after 30 min, but other patients have some residual activity up to 2 h exposure. Landon and Toothill (1986) found methionine synthase activity in human placenta to be normal following delivery after Caesarean section with nitrous oxide exposure of less than 25 min up to the time of delivery of the placenta.

For exposures lasting 4 h, the dose–response curve in the rat (Koblin et al., 1981) indicates an ED_{50} of about 10% nitrous oxide. Concentrations in use in clinical anaesthesia (usually 50–70%) are therefore on the upper flat part of the dose–response curve and there should be no major differences attributable to the concentration of nitrous oxide selected within this range. The dose–response curve has not been determined for man.

Plasma methionine concentration. This has been considered above. There are no changes during the first 3 h of anaesthesia with nitrous oxide in man (Nunn, Sharer et al., 1986), but values were 30% of those before operation after 8 h and 20% after 24 h (Skacel et al., 1983). S-Adenosyl methionine was unchanged after 3 h.

Deoxythymidine synthesis. There is agreement that there are grossly abnormal values for the dU suppression test with megaloblastic marrow in man after 24 h exposure to nitrous oxide (Amess et al., 1978; O'Sullivan et al., 1981; Skacel et al., 1983). O'Sullivan and colleagues (1981) reported abnormal marrow in four of five patients exposed to nitrous oxide for 12 h.

There is a difference in the findings reported after shorter exposures. O'Sullivan found no abnormalities of marrow in 30 routine surgical patients who had received nitrous oxide for less than 6 h. However, Amos and colleagues (1982) reported abnormal dU suppression tests and megaloblastic marrow in a large series of patients who received nitrous oxide for 6 h or less (fig. 5). Their patients all required intensive therapy and raise the possibility that the compromised patient may be more sensitive to nitrous oxide. They reported that 18 of the 22 megaloblastic patients died. A patient with a severe haemorrhage was found to have an abnormal dU suppression and megaloblastic marrow after exposure to nitrous oxide for only 2 h (Nunn, Chanarin et al., 1986). Kano and colleagues (1981) found abnormal dU suppression tests in some patients after 4 h exposure to nitrous oxide and no normal values in exposures of more than 7 h.

We must conclude from these data that interference with thymidine synthesis is to be expected in man after 12 h of exposure to nitrous oxide, but may appear within 2 h or even less.

Number of patients	13	20	9
Mean ± SEM	7.9±0.8	11.9±1.1	21.3±2.9

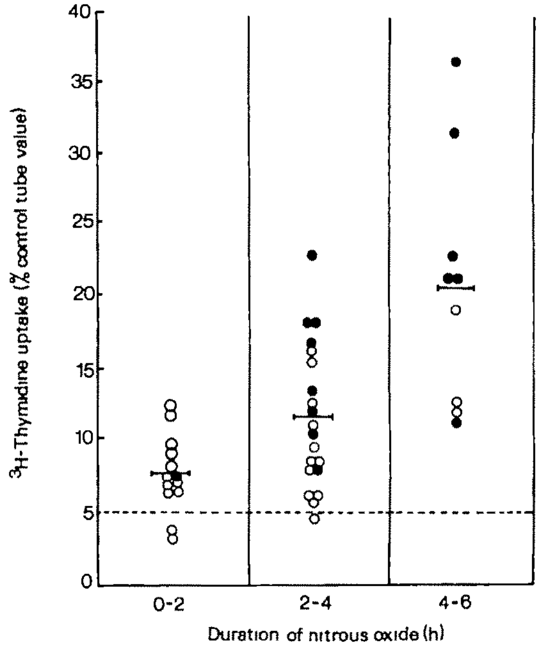

FIG. 5. Postoperative deoxyuridine suppression tests (expressed as ^{3}H-thymidine uptake) in patients who had received nitrous oxide for different durations. ● = Megaloblastic marrow. Values over 5% are abnormal from these authors' laboratory. Reproduced with permission from Amos and colleagues (1982).

There is considerable individual variation and the sick patient may be more susceptible.

Biochemical correction of the effects of nitrous oxide

Methionine. It is possible to supply methionine by the oral route to cover any shortfall resulting from loss of activity of methionine synthase. This was investigated in relation to a neurological condition resembling subacute combined degeneration of the cord, induced in monkeys by chronic exposure to 15% nitrous oxide (Scott et al., 1981). Supplementation of diet with methionine 2 g daily greatly reduced the demyelination and neurological damage which was seen in the monkeys which did not receive the dietary supplementation.

Folinic acid. The administration of folinic acid (5-formyl THF) cannot restore the concentrations of either of the products of the methionine synthase reaction, but it can restore deoxythymidine synthesis. The required dose in man is large. However, there is now very strong evidence that 30 mg twice daily will prevent development of an abnormal dU suppression test and megaloblastic marrow changes in some, but not all, patients during prolonged exposure to nitrous oxide (O'Sullivan et al., 1982; Skacel et al., 1982 (supplement to letter); Amos et al., 1984; Kano et al., 1984; Nunn, Chanarin et al., 1986). Reference has been made above to the mitigation of the fetotoxic effects of nitrous oxide in rats by pre-treatment with folinic acid (Keeling et al., 1986). Kano and colleagues have also reported that methylcobalamin at the end of operation corrected the abnormal dU suppression tests. This unexpected finding suggests that the bond between the methionine synthase apoenzyme and oxidized vitamin B_{12} may be broken. It is to be expected that any B_{12} preparation administered *during* exposure to nitrous oxide would be rapidly oxidized to bivalent cobalt.

CONDITIONS REQUIRING SPECIAL CONSIDERATION WHEN NITROUS OXIDE IS USED

The final section of this paper considers specific situations in which nitrous oxide may be administered. In some cases nitrous oxide appears to be contraindicated, while in others it appears to be harmless. However, there are many situations in which it is not yet possible to form a clear opinion. It must be stressed that this review only considers the interaction between nitrous oxide and vitamin B_{12}. It does not consider other properties of nitrous oxide which might influence its choice as the best anaesthetic agent in a particular situation.

Administration lasting more than 24 h

Gross interference with DNA synthesis is to be expected after 24 h of administration (Amess et al., 1978; Skacel et al., 1983) and production of granulocytes will be seriously impaired. In patients with normal bone marrow, stores of mature granulocytes will normally be adequate to prevent leucopaenia for up to about 3 days. Beyond that time, however, leucopaenia will usually develop and agranulocytosis has been reported after 5–7 days (Lassen et al., 1956; Wilson, Martin and Last, 1956).

There would seem to be an absolute contraindication to the continued use of nitrous oxide after 24 h, although the precise upper limit of safe duration cannot be deduced from existing data and is probably variable from one patient to another, depending *inter alia* on marrow stores of granulocytes. If there are very strong indications for the continued use of nitrous oxide, there is good evidence (outlined above) that protection from megaloblastic changes can be obtained, in most but not all patients, with folinic acid 30 mg twice daily. Since efficacy does not seem to be 100%, it is important to monitor with daily full blood counts.

24-Administration

A reasonably healthy surgical patient appears able to receive nitrous oxide for 24 h without overt harm, although there will almost certainly be megoloblastic marrow changes and an abnormal dU suppression test. None of the patients reported by Amess and colleagues (1978) became leucopaenic in the postoperative period. However, in two patients reported by Skacel and colleagues (1983), the neutrophil count decreased to 1×10^9 litre^{-1} between the 2nd and 4th days. These changes can usually be prevented by the use of folinic acid. The excellence of the analgesia provided by nitrous oxide may well be considered to outweigh the haematological problem in the healthy surgical patient.

Administrations lasting less than 24 h

It seems likely that in man, in contrast to the rat, exposure of less than 30 min will not cause any measurable change in hepatic methionine synthase activity. In combination with a wealth of clinical experience, this suggests that there is no special hazard for short exposures to nitrous oxide. There is a variable response to exposures lasting between 30 min and 2 h. However, it now seems likely that exposures of more than 2 h are likely to cause interference with hepatic methionine synthase activity. The paucity of human data makes it more difficult to say how long an exposure is required to cause significant interference with DNA synthesis. It is likely that there will be considerable individual variation and results obtained in healthy patients cannot be extrapolated to the patient who is seriously ill. Nevertheless, it seems likely that, once methionine synthase activity is inhibited, it will remain so for some days. It is therefore possible than an abnormal dU suppression test may develop after the end of surgery and exposure to nitrous oxide. This has not been investigated in man.

Repeat exposures to nitrous oxide

Since the inhibition of methionine synthase is rapid and its recovery slow (Deacon et al., 1980), it is to be expected that exposure repeated at intervals of less than 3 days will have a cumulative effect. A patient exposed to Entonox (50 % nitrous oxide + 50 % oxygen) for 15 min three times a day twice developed an abnormal dU suppression test and megaloblastic marrow changes after total exposures of about 2 weeks (Nunn et al., 1982).

Megaloblastic marrow and an abnormal dU suppression test were found at the start of an anaesthetic given 7 h after a previous anaesthetic with nitrous oxide lasting 2 h (Nunn, Chanarin et al., 1986). Nitrous oxide was given a second time, but with 30 mg of folinic acid, after which the marrow was found to be normal.

There appear to be no other biochemical studies after repeat anaesthetics in man. However, clinical experience suggests that the outcome is often more favourable than might be expected, particularly in children who often require repeated anaesthetics. R. M. Jones (personal communication) has kindly supplied data on three children who have recently had 25–40 daily administrations of nitrous oxide for radiotherapy, each lasting aboout 20 min. Leucocyte counts in peripheral blood have remained unchanged.

The sick patient

Reported results for the dU suppression test tend to show abnormalities after shorter exposures to nitrous oxide in "sick" patients, compared with relatively healthy surgical patients. The patients reported by Amos and colleagues (1982) were all sufficiently "sick" to be admitted to Intensive Care and included 50 patients who had received nitrous oxide for durations up to 6 h. Of these patients, 48 had abnormal dU suppression tests and 18 had megaloblastic marrow—even one who had received nitrous oxide for less than 2 h. This was also seen in the case report described above (Nunn, Chanarin et al., 1986). These findings contrast with those of O'Sullivan and colleagues (1982) who, in relatively healthy patients, observed no abnormal marrows when the duration of exposure to nitrous oxide was 6 h.

It thus seems quite likely that the safe period of exposure to nitrous oxide is influenced by the preoperative state of the patient, but it is difficult to be more precise. There is, again, a paucity of human data and great difficulty in defining what we mean by "sick".

There may be considerable clinical relevance in megaloblastic changes occurring in the postoperative period in the sick patient. In Amos' series, 16 of 18 patients with megaloblastic changes died while in the Intensive Care Unit. This may be compared with a mortality of only seven of 22 patients who remained normoblastic in spite of having received nitrous oxide. It is generally recognized that mortality during intensive care is related to the number of systems in failure and marrow failure may be sufficient to tip the balance in a patient who already has multi-system failure.

There are no data on the additional risk imposed by using nitrous oxide for anaesthesia in a patient who is gravely ill. A typical example would be the closure of a stress ulcer in a patient with multisystem failure. This is clearly a very difficult field for a controlled randomized prospective trial, but that is the only way that answers, in terms of clinical relevance, will emerge.

Wound healing and infection

It would seem that interference with DNA synthesis might be unfavourable for wound healing. An animal study by Algie and colleagues (1984) failed to show any adverse effect of nitrous oxide. It would be valuable to determine whether there is any effect of nitrous oxide on the ability of a patient to survive a severe infection, but a trial to test this hypothesis would be a formidable undertaking and no reports are yet forthcoming.

Pregnancy

The demonstration of no change in placental methionine synthase activity following the use of nitrous oxide at Caesarean section suggests that it is unlikely that the fetus would be affected by the short duration of exposure (Landon and Toothill, 1986). The definitive experiment would be a study of the fetal liver following delivery, but ethical considerations would seem to exclude this investigation. Changes in the rat fetal liver (Baden, Serra and Mazze, 1984) are probably not relevant because of the very different rate of inactivation of human and rodent methionine synthase.

The use of nitrous oxide during early pregnancy presents a very difficult problem. On the one hand, there is irrefutable evidence that nitrous oxide is a mild teratogen in the rat and its partial reversal with folinic acid suggests very strongly that the mechanism is interference with deoxythymidine synthesis, secondary to inhibition of fetal methionine synthase activity (Keeling et al., 1986). On the other hand, a very large body of human epidemiological evidence (cited above) has failed to find any increase in the incidence of fetal abnormalities following anaesthesia in pregnancy. There are three possible explanations. First, there may be a species difference and this cannot be directly tested. Second, most anaesthetics given in pregnancy are of short duration and may be too short to affect fetal methionine synthase activity. Third, the commonest procedure requiring an anaesthetic in pregnancy is cervical suturing and this is usually undertaken after most major organogenesis is completed.

The potentially dangerous situation would be an anaesthetic lasting several hours and administered within the first 4 weeks of pregnancy. There is one report of a normal fetus delivered after the mother received nitrous oxide for 2 h approximately 2 weeks after conception (Park, Fulton and Shelley, 1986). Clearly, this is an uncommon event and it will take a long time to assemble a sufficient number of such cases to permit a conclusion to be drawn on the risk. In the meantime, it is the view of the author that the use of nitrous oxide in pregnancy during the period of organogenesis is inadvisible in the light of present knowledge. There are a large number of alternative anaesthetic agents for which there is no convincing evidence of teratogenic potential.

An alternative approach would be to cover the administration of nitrous oxide during early pregnancy with folinic acid, following the animal studies reported by Keeling and colleagues (1986). This has been considered by Marx (1985), and there is no obvious objection to the practice.

Exposure to trace concentrations

The dose–response curve for nitrous oxide on methionine synthase activity is displaced to the left by increasing durations of exposure (Sharer et al., 1984). In the rat, maximal sensitivity occurred after 48 h exposure and the ED_{50} for inhibition of hepatic methionine synthase was then about 5000 parts per million (p.p.m.). The lowest concentration at which partial inhibition could be detected was 1000 p.p.m. and no changes were detected at 450 p.p.m. These values are generally above concentrations recorded in operating theatres, even without scavenging equipment, and they are far above the low concentrations which can be attained with scavenging (Davenport et al., 1980). Normal serum methionine concentrations have been reported in staff working in badly contaminated operating theatres (Nunn et al., 1982). It seems unlikely that normal work in operating theatres exposes staff to any danger arising from inactivation of vitamin B_{12}. It should, however, be stressed that the dose–response curve for chronic exposure was prepared for rats and it is difficult to see how it could be determined in man.

Dental operations are a different matter and much higher levels of contamination have been reported, sometimes in excess of 5000 p.p.m. (Hillman et al., 1981). The difference is attributable to high flow rates of nitrous oxide and poor ventilation. Sweeney and colleagues (1985) reported three instances of abnormal dU suppression test in the bone marrow of 20 dentists using nitrous oxide for analgesia. Two dentists had hypersegmented polymorphs in their peripheral blood.

Abuse of nitrous oxide

The report of Layzer (1978) makes chilling reading. Fifteen patients had been inhaling subanaesthetic concentrations of nitrous oxide for long periods of time, 14 of them intentionally. All had a condition resembling subacute combined degeneration of the cord, which in most cases responded to abstinence from nitrous oxide. Other unpublished examples have been reported to the author and there seems no doubt that this is an established consequence of the abuse of nitrous oxide. Scott and colleagues (1981) reported a similar condition in monkeys which responded to supplementation of dietary methionine. The parallel with deficiency of vitamin B_{12} would suggest that folinic acid would be ineffective. The possibility of abuse of nitrous oxide should be considered in any patient with access to the gas who reports signs and symptoms resembling subacute combined degeneration of the cord.

The patient with subclinical B_{12} deficiency

It would not be surprising if a patient with subclinical vitamin B_{12} deficiency should develop symptoms following administration of nitrous oxide, which presumably inactivates stores of vitamin B_{12} as well as B_{12} bound to methionine synthase. Schilling (1986) has recently reported two women who developed neurological dysfunction consistent with subacute combined degeneration of the cord within 8 weeks of being anaesthetized with nitrous oxide. One had a previous ileal resection for Crohn's disease and the other had pernicious anaemia. O'Leary, Combs and Schilling (1984) have demonstrated, in animals, synergism between vitamin B_{12} deficiency and exposure to nitrous oxide.

The only source of vitamin B_{12} in man is dietary intake from animal products. Strict vegetarians may have a subclinical deficiency and might prove to be at risk from nitrous oxide administration.

Methotrexate therapy

It has recently been suggested that nitrous oxide may complicate methotrexate therapy in children. Ueland and colleagues (1986) concluded that it might reduce the therapeutic effect and increase side effects. However, this theoretical problem has not yet been investigated.

CONCLUSIONS

If nitrous oxide were to be introduced as a new drug, the metabolic effects outlined above would raise grave doubts about its acceptability. Eger (1985) has presented the case against nitrous oxide. He included a range of adverse effects, but the most serious are based on the interaction with vitamin B_{12}. Eger himself (personal communication) has now abandoned the use of nitrous oxide in routine clinical anaesthesia. The alternative case in favour of the continued use of nitrous oxide has been presented by Saidman and Hamilton (1985). They make the telling point that, except in the case of prolonged administration, inhibition of methionine synthase has not produced a clinical effect recognized by generations of skilful observers.

The contradiction between the serious biochemical effects of nitrous oxide and the apparent absence of adverse clinical effects in routine anaesthesia makes it difficult to draw firm conclusions. On the one hand, some may feel that the biochemical effects require that nitrous oxide should be adandoned in favour of alternative anaesthetics, of which there are plenty. On the other hand, the vast majority of anaesthetists, including the author, are influenced by the paucity of information on adverse outcome and continue to use such a well tried agent. The truth probably lies between these two extreme viewpoints. Evidence has been presented for believing that nitrous oxide may be quite harmless when used for a limited duration in patients without adverse predisposing factors. The definition of a safe duration is a difficult problem and is considered above. What are the adverse predisposing conditions is an even more difficult question. The more obvious factors have been considered, but a great deal of difficult and detailed clinical study will be required to define those conditions in which nitrous oxide may be contraindicated.

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ADVERSE EFFECTS OF VOLATILE ANAESTHETICS

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There is little question that all chemical substances capable of producing the state of anaesthesia may be classified as toxins. Such toxicity is within the limits of acceptability and is usually totally reversible. Depression of ventilation, cardiac function, CNS function and renal perfusion are recognized consequences of the state of general anaesthesia. These actions are ephemeral, disappearing soon after termination of administration of the inhalation anaesthetic.

Obviously, reversible depression of organ systems is not imputed when toxicity of these drugs is mentioned. True organ toxicity is often irreversible, fatal and totally unexpected. Table I outlines some of the viscerotoxicities in which inhalation anaesthetics have been implicated. The theme of this review is viscerotoxicity initiated by biotransformation of the halogenated anaesthetics. Thus from a pragmatic standpoint, hepatic and renal viscerotoxicity of halogenated anaesthetics will be the primary focus of discussion.

A BRIEF HISTORICAL BACKGROUND

The first recorded case of unexplained jaundice following chloroform anaesthesia occurred in 1848 (Defalque, 1968), only 1 year after introduction of this halogenated drug to clinical practice by Simpson. There was fairly widespread knowledge that inhalation of chloroform could be followed in a small percentage of patients by "delayed chloroform poisoning". Ether was exonerated from this association. Continued difficulties with chloroform produced a prohibition of its use by the Committee on Anesthesia of the American Medical Association in 1912 (Henderson, Cullen and Martin, 1968). Later studies indicated that the cause and effect association between chloroform and jaundice is more recondite than previously believed. Siebecker and colleagues (1960) reported 1210 anaesthetics with chloroform which resulted in only one fatal case of hepatic necrosis. This report, and others throughout the years indicate that, although there does appear to be a fairly clear association between chloroform administration and post-anaesthetic hepatic viscerotoxicity, the attack rate is not universal. The logical implication is that chloroform may not be a direct hepatotoxin, but rather produces damage via more complex mechanisms subject to considerable individual variations.

TABLE I. *Visceral toxicities ascribed to inhalation anaesthetics*

A. Chronic exposure
  (1) Teratogenicity; abortifacient
  (2) Neurological disease
  (3) Bone marrow depression
  (4) Hepatic necrosis

B. Acute exposure
  (1) Renal failure
  (2) Hepatic necrosis
  (3) Immunosuppression

Trichloroethylene

A classic halogenated hydrocarbon, trichloroethylene is still available in the U.K., although not in the U.S. Evidence concerning the potential for universal hepatotoxicity of this drug is unconvincing at best, unsettling at worst. It would be expected that a substance which was used as commonly as trichloroethylene, not only as an anaesthetic but also as a commercial solvent and dry cleaning agent, would have its toxicity well delineated. Unfortunately this is not the case, as stated by Dykes (1980): "...it appears that the only reasonable conclusion to be reached is that it is currently impossible to evaluate the hepatotoxic potential of trichloroethylene in man because of

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the utter lack of acceptable evidence." However, its hepatotoxicity in animal studies is well documented (Waters, Gerstner and Huff, 1977).

Fluroxene (trifluoroethyl vinyl ether)

This is an anaesthetic which never gained a great following in either the U.S. or the U.K. Interestingly, it was the first fluorinated anaesthetic. Most retrospective non-controlled clinical series failed to make an association with postoperative jaundice (Cannon and Dornette, 1964). In fact, this drug was used as the anaesthetic of choice for the early series of liver transplants (Aldrete, LeVine and Gingrich, 1969). A case report in 1972 implied that hepatotoxicity might be linked with the anaesthetic, particularly if biotransformation were enhanced by hepatic microsomal inducing drugs (Reynolds, Brown and Vandam, 1972). Animal studies by Harrison and Smith (1973) ostensibly confirmed this anecdotal clinical observation.

Halothane

Introduced to clinical practice in 1956, halothane was heralded as a true breakthrough in anaesthesia drugs because of its potency, lack of flammability and general smoothness of administration. Animal studies at that time failed to demonstrate any hepatic injury (Stephen et al., 1958). An explosive increase in the clinical use of halothane quite rightly followed advent of the drug. Initial clinical use indicated little or no adverse liver actions. However, case reports of unexplained jaundice following anaesthesia with halothane began to surface (Virtue and Payne, 1958; Lindenbaum and Leifer, 1963). Many in the anaesthesia community discounted these cases as originating from viral hepatitis or other aetiological factors, since a true cause and effect relationship had not been established. At least 350 putative cases of "halothane hepatitis" had been reported by 1963, 5 years after widespread international use of the drug. Small scale retrospective studies led to no resolution of the issue (Dawson et al., 1963; Mushin et al., 1964). The question of safety of halothane was most important in the mid-1960 era as it was then the most commonly used anaesthetic in Western nations. This fact led to one of the largest epidemiological studies of all times, the U.S. National Halothane Study sponsored by the National Institutes of Health (National Halothane Study, 1969). The unfortunate result of this massive study was that it was totally inconclusive. There were several intrinsic problems associated with the investigation which prejudiced the results: (1) it was retrospective; (2) it was non-randomized; and (3) several of the reporting institutions had already previously published anecdotal case reports implicating halothane in postoperative jaundice. One conclusion that could be drawn from the study was that severe hepatic necrosis following halothane anaesthesia was not a common occurrence.

Methoxyflurane

Similar to fluroxene, this drug was introduced in 1962. It was more popular with U.S. than with U.K. anaesthetists. In 1966, methoxyflurane was linked to a high output renal toxicity (Crandell, Pappas and MacDonald, 1966). The association of renal toxicity with this anaesthetic was demonstrated conclusively and the pathology was shown to result from the biotransformation of the compound into inorganic fluoride which subsequently poisoned renal tubules in a dose-related manner (Mazze, Shue and Jackson, 1971; Cousins and Mazze, 1973). The clinical use of this anaesthetic is today quite minimal, secondary to this well-understood and well-proven toxic effect.

EPIDEMIOLOGY OF HALOGENATED ANAESTHETIC VISCEROTOXICITY

There are several predisposing factors implicated as increasing the risk of viscerotoxicity of volatile halogenated anaesthetics: multiple exposures, obesity, middle age, gender and ethnic origin. Specific attention will be given to those circumstances which are thought contributory to halothane hepatic injury.

Multiple exposures. Sufficient data exist to indicate strongly that re-exposure to halothane is associated with a higher incidence of unexplained hepatic problems than is a single anaesthetic with the drug (Inman and Mushin, 1974; Moult and Sherlock, 1975; Benjamin et al., 1985). More than 80 % of patients examined have had more than one exposure to halothane. The time of maximal susceptibility in this regard is not well documented, although 28 days seems to be a recurrent interval (Neuberger and Williams, 1984). Trowell, Peto and Crampton-Smith (1975) examined in prospective fashion 18 patients with carcinoma of the cervix who were administered repeated halothane anaesthetics for radiation therapy and compared them with 21 cohort patients who were anaesthetized with nitrous oxide. The halothane group were noted to have increased post-anaesthetic transaminase concentrations and two had liver biopsies indicating mild hepatitis. Although none of these individuals developed frank hepatitis or liver necrosis, the authors urged caution and use of screening for transaminase concentration if multiple halothane anaesthetics are required during the course of treatment. The mystery was heightened because a study set up in like fashion by Allen and Downing (1977) in South African black women failed to show increased transaminase concentrations under similar circumstances.

Obesity. Obesity has been implicated in several reports as increasing the risk of halothane hepatic dysfunction after operation (Peters et al., 1969; Walton et al., 1976). In obese patients who develop unexplained hepatitis following halothane anaesthesia, the prognosis ostensibly is not as good as in patients of near ideal weight. A prospective study indicated that obese patients who received short-interval multiple administrations of halothane increased the possibility of post-anaesthetic increase in transaminases (Dundee et al., 1981). None of their 129 patients in the 3-year study exhibited frank hepatic necrosis; rather, hepatic injury was reflected only as increases in transaminase concentration.

Middle age. Halothane-associated jaundice is rare in the young or aged. Thus halothane remains the premier paediatric anaesthetic worldwide, even in the U.S. where its use is extremely constrained because of medico-legal implications. In fact, repeat halothane anaesthetics in infants and pre-pubertal children has never been considered a hazard. Middle age seems to be a primary target for age-related risk factors (Carney and Van Dyke, 1972; Cousins, Plummer and Hall, 1984). Consensus is that peak middle age is 40–50 yr in this circumstance.

Gender. Females ostensibly are at greater risk than males by approximately 2:1 (Benjamin et al., 1985).

Genetics and ethnic origin. Halothane hepatitis has been reported in three pairs of closely related women with a common ethnic origin, Mexican-American (Hoft et al., 1980). Data of this nature are indicative of a pharmacogenetic aetiology of the problem. Further indication of a basic drug-metabolic inherited attribute has come from the work of Farrell, Prendergast and Murray (1985). These authors demonstrated that there co-exists a basic deficit in white cell detoxification ability in those individuals with propensity to develop hepatitis following halothane, but the results have not been confirmed by other groups as yet. However, genetics may certainly play a role in this problem (Cousins et al., 1981).

Because of the extremely sporadic and unpredictable nature of post-halothane liver complications, coupled with the Sisyphean task of accurate diagnosis, post-halothane "hepatitis" diagnoses are conjectural at best. An overall incidence of 1 per 10000 halothane administrations is a figure commonly accepted (Bottinger, Dolen and Hallen, 1976; Strunin and Davies, 1983). It is interesting to note that this rate is considerably lower than the incidence of unexpected liver disease found by routine laboratory testing of elective surgical admissions. Schemel (1976) found 11 otherwise healthy patients (ASA I) admitted for elective surgery who had abnormal liver function studies, in 7620 individuals studied. Surgery was cancelled in these 11 pending further investigation. Three persons became clinically jaundiced, an incidence of 1:2540 patients. Clearly this number is four times higher than the purported attack rate of halothane hepatitis! Diagnosis is compounded by lack of specific morphological alterations (Benjamin et al., 1985) and the very common failure to pursue additional laboratory studies when confronted with a patient exhibiting unexplained post-surgical jaundice (Douglas et al., 1977). An analysis of epidemiological features of more than 700 presumed cases of halothane hepatitis extracted from various reports is given in table II.

THE BASIS OF CHEMICAL HEPATOTOXICITY

Biotransformation of a chemical to a reactive metabolite is well known in pharmacology. This "bioactivation" process has been documented with numerous hepatotoxins. Using carbon tetrachloride as an example, it is now clear that the hapatotoxicity of carbon tetrachloride depends on the cleavage of the carbon–chlorine bond via biotransformation (Recknagel, 1967). The biotransformation of carbon tetrachloride is mediated by the hepatic microsomal cytochrome P-450

TABLE II. *Unexplained jaundice following halothane anaesthesia in 701 patients collated from reports: the percentage incidence of relevant factors and the days to onset of clinical jaundice. (Adapted from Cousins, Plummer and Hall (1984).)*

Age	
Younger than 20 yr	2%
20–40 yr	37%
Older than 40 yr	61%
Females	63%
Obesity	62%
Multiple exposures	74%
Mortality rate	54%
Days to onset of clinical jaundice	
Single exposures	8.3 days
Multiple exposures	5.7 days

system. The product of the cleavage is trichloromethyl radical, which can initiate a series of lipid peroxidation events resulting in subcellular membrane damage and cellular necrosis of the hepatocytes. Substances which inhibit the biotransformation of carbon tetrachloride decrease toxicity, whereas stimulation of the biotransformation process results in increased toxicity. As with many hepatotoxins, a specific liver zonal necrosis is noted with carbon tetrachloride. Since the centrilobular hepatocytes contain the highest concentration of cytochrome P450 in the liver, they consequently produce higher concentrations of free radicals and are the first hepatocytes injured, producing a centrilobular necrosis. The biotransformation of carbon tetrachloride results in a chemical reduction of the parent compound rather than the chemical oxidation usually observed during biotransformation. This reductive process is of interest, though, since halothane undergoes reductive metabolism.

Chloroform produces liver injury in animals in a fashion similar to that observed with carbon tetrachloride. Inhalation of 1% chloroform in oxygen by rats for 1 h does not usually lead to liver necrosis. However, if the animals are pretreated with phenobarbitone to induce the hepatic biotransformation enzymes, marked hepatotoxicity is produced by this exposure (Brown, Sipes and Sagalyn, 1974). Depletion of hepatic glutathione has also been shown to make animals susceptible to chloroform-induced hepatotoxicity. Chloroform has been shown to be oxidatively biotransformed by the cytochrome P450 system in the centrilobular hepatocytes, to phosgene (Pohl, Martin and George, 1980). Phosgene is an extremely reactive chemical that attacks sulphydryls. When the natural protection afforded by the presence of high concentrations of glutathione are exceeded by increased formation of phosgene from chloroform (induction) or the glutathione concentrations are suppressed experimentally, the phosgene attacks cellular protein sulphydryls. Since protein sulphydryls are critical to membrane integrity and many protein functions, a "biochemical lesion" develops and the compromised hepatocyte dies.

Almost all the biotransformation known to occur with volatile anaesthetics is via oxidative pathways. Halothane is the one exception, since it is known also to undergo reductive biotransformation. The examples with carbon tetrachloride and chloroform serve as models of hepatotoxins that are toxic as a result of their biotransformation. With both compounds, two aspects are necessary for them to be toxic. First is lack of refractoriness to biotransformation. In other words, they serve as substrates for the biotransformation enzymes and a significant portion of the parent compound is metabolized. Second, the products of their biotransformation, whether intermediates or primary metabolites, are *reactive* with cellular macromolecules. This has been the quest with volatile anaesthetics—are they biotransformed and do they form reactive products?

BIOTRANSFORMATION OF HALOTHANE

Unfortunately, it was not until halothane had been used clinically for at least 6 years that there was evidence that the anaesthetic is biotransformed (Van Dyke, Chenoweth and Van Poznak, 1964). Before this time it had been taught categorically that halothane—in fact, all inhalation anaesthetics except trichloroethylene—was metabolically unaltered by the body's biochemical machinery. Later studies in man indicated that a somewhat surprising 18% of absorbed halothane is biotransformed (Rehder et al., 1967). The major metabolite of halothane biotransformation in both man and animals is trifluoroacetic acid. In addition Cohen and others (1975) found a variety of halothane metabolite conjugates in humans, including trifluoroacetyl ethanolamine and N-acetyl-S-(2-bromo-2-chloro-1,1-difluoroacetyl)-L-cysteine. These metabolites are oxidatively derived. Since oxidation is a major pathway of drug biotransformation, it seemed quite fitting that attention was initially directed to these metabolites. None of the oxidative metabolites identified is truly toxic *per se*, nor is their presence indicative of free radical production. In fact, induction of oxidative halothane metabolism by phenobarbitone pre-treatment does not predispose to hepatic necrosis following halothane anaesthesia, as it does with chloroform (Brown, Sipes and Sagalyn, 1974). Oxidative and conjugation pathways of halothane were considered and examined, but non-oxygen dependent (reductive) biotransformation was not considered until later. Uehleke, Hellmer and Taberelli-Poplawski (1973) discovered that covalent binding of halothane metabolites to liver protein and lipid *in vitro* was accelerated in the presence of a nitrogen atmosphere. Subsequent studies found that the binding could be greatly enhanced if the *in vitro* or *in vivo* studies were performed with phenobarbitone pretreated animals. Interestingly, fluoride ion was found to be cleared from the halothane molecule under reductive biotransformation conditions which correlated to covalent binding of halothane metabolites *in vivo* (Van Dyke and Gandolfi, 1976; Widger, Gandolfi and Van Dyke, 1976). Thus serum fluoride became a simple indicator of the reductive biotransformation of halothane. The corresponding product of the reductive defluorination of halothane was found to be 2-chloro-1,1-difluoroethylene (Mukai et al., 1977). In addition, a non-defluorinated metabolite resulting from reductive biotransformation was also formed: 2-chloro-1,1,1-trifluoroethane. Neither of these metabolites was found to be toxic *per se*, but the process of their information produces radicals which may covalently bind to liver macromolecules. Both metabolites have been unequivocally demonstrated to be produced in man (Gourlay et al., 1980).

Predicated on the *in vitro* reductive biotransformation of halothane profile, an animal model of hepatic necrosis was developed (McLain, Sipes and Brown, 1979). Specifics of the model, include pretreatment with phenobarbitone followed by anaesthesia with halothane (1% v/v) in a mildly hypoxic environment ($F\text{I}_{\text{O}_2} = 0.14$). It was found under these circumstances that centrilobular hepatic damage was produced, paralleled by increases in reductive metabolites of halothane.

Biotransformation via the reductive cytochrome P450 mediated pathway is probably not the proximate cause of the phenomenon of severe hepatic necrosis following halothane anaesthesia in man. There are several reasons to suspect this: (1) the effect of reductive metabolism of halothane in animals is ephemeral and not severe; (2) biotransformation via the reductive pathway is common; (3) hypoxia is usually not a prominent event in human halothane hepatitis.

There are studies which attempt to implicate hypoxia as a common feature for all hepatic necrosis following anaesthesia in animal models and by extrapolation, to man (Shingu, Eger and Johnson, 1982; Shingu et al., 1983). There is no question that all anaesthetic techniques decrease hepatic blood flow in proportion to decreases in systemic arterial pressure, including extradural block. However, the concept of pure hypoxic damage as a common cause of anaesthetic-induced hepatic necrosis is probably erroneous in light of the following reasons:

(1) Cousins and his co-workers have developed an anaesthetic toxicity model for halothane in guineapigs where no hypoxia is required (Lunan, Cousins and Hall, 1985).

(2) Even in these hypoxic models, halothane is distinctively different from the other anaesthetics. Shingu, Eger and Johnson (1982) and Shingu and colleagues (1983) found that the other anaesthetics were "toxic" only in phenobarbitone pre-treated animals at an $F\text{I}_{\text{O}_2}$ of 0.10 or less, while halothane is toxic at $F\text{I}_{\text{O}_2}$ 0.14.

(3) Free radical scavengers block the necrosis, as do metabolic inhibitors; without phenobarbitone induction the lesion does not occur (Jee et al., 1980).

(4) It is rare that liver necrosis is the primary and sole untoward event seen with hypoxia episodes in man.

(5) The chronology of the appearance of the liver lesion and the type of lesion produced differ from that produced by halothane and that produced by hypoxia (Lind et al., 1985).

(6) Female rats have been resistant to liver injury by halothane. Female rats biotransform less halothane but are not known to be less susceptible to hypoxia (Plummer et al., 1985).

The animal models which have been developed may or may not be applicable to the problem of human hepatotoxicity. They have given a great deal of insight to and understanding of the issues involved. It is of interest that the models display considerable sex, age, species and strain differences insofar as susceptibility to hepatic necrosis is concerned. The rat and guineapig display hepatotoxicity, whereas the mouse and dog do not. The rat has been extensively investigated in this regard. Female rats, and non-adult animals of either sex do not display hepatic necrosis when induced with phenobarbitone and anaesthetized with halothane at $F\text{I}_{\text{O}_2}$ 0.14 (Jee et al., 1980). Strain sensitivity has been demonstrated among rats. This leads to the conclusion that there exist considerable genetic differences regarding sensitivity to hepatic destruction, probably mediated via different pathways of biotransformation of halothane (Cousins et al., 1981).

IMMUNOLOGICAL ASPECTS OF HALOTHANE TOXICITY

Early in the recognition of halothane-associated liver complications, it was suggested that adverse reactions in the liver could be an allergic or hypersensitivity phenomenon. There were certainly several features of the problem which gave certain credence to this concept:

(1) Multiple administrations caused both increased incidence and an increased intensity of hepatic lesions.

(2) Antimitochondrial antibodies were detected in some patients in whom halothane was thought responsible for their jaundice (Rodriguez et al., 1969).

(3) Two individuals "sensitive" to halothane were exposed to sub-anaesthetic concentrations of the anaesthetic and soon afterwards developed increasing transaminases (Belfrage, Ahlgren and Axelson, 1966; Klatskin and Kimberg, 1969).

(4) Reports that lymphocytes were sensitized to halothane in patients who had experienced halothane hepatitis (Paronetto and Popper, 1970).

(5) It is difficult to understand the mechanism of an allergic reaction caused by the non-protein small molecule such as halothane.

Subsequent laboratory and clinical investigation, though, did not clearly support a role of the immune system in halothane-induced liver injury. A new perspective in such potential hypersensitivity reaction mechanisms came about with the demonstration of biotransformation and bioactivation of halothane. The finding that metabolites could bind covalently to liver tissue is important, since such complexes can potentially act as haptens and evoke an immune response. Understandably a number of workers focused on attempting to demonstrate hepatic lesions, in animals, produced by sensitizing them with halothane metabolite–protein complexes and subsequently administering halothane anaesthesia. Although the concept was a refulgent example of logical scientific reasoning, no hepatic lesions were produced (Reves and McCracken, 1976).

Further animal studies implied that the immunogenic material resulted from the oxidative biotransformation of halothane (Neuberger et al., 1981). Studies at the U.S. National Institutes of Health (Satoh et al., 1985) and our Institute (Callis et al., 1986) indicated that the oxidative biotransformation of halothane produces trifluoroacetyl chloride which covalently binds to the lysine residues on proteins. This altered liver protein acts as an antigen, and antibodies are produced. The antibodies can be detected in immunological assays by using trifluoroacetylated carrier protein (albumin) as a representative antigen. In human and animal studies these antibodies have been found to be specific for the trifluoroacetyl moiety (Vergani et al., 1980). Thus, in summary, oxidative biotransformation of halothane produces an intermediate which binds to liver tissue and can produce an immune response in certain individuals.

Further extensions of these studies have found that rabbits exposed repeatedly to halothane at 5-week intervals produce antibodies against the trifluoroacetyl carrier protein. Peak antibody concentrations are obtained after three exposures. In addition, the specificity of the antibodies towards the synthetic antigen changes with time and subsequent halothane exposures. Evidently, the endogenous antigenic material is being more recognized than the synthetic antigen.

Interestingly, Pohl, Martin and George (1980) have found that one of the endogenous proteins acylated by the trifluoroacetyl moiety is cytochrome P450 (Satoh et al., 1986). Particularly, this is a cytochrome P450 associated with the liver cell plasma membrane.

The antibody produced by halothane exposure seems to be rather specific at this time, since anaesthesia personnel with long-term exposures to low concentrations of halothane do not demonstrate it, nor do patients with no liver damage following routine halothane anaesthesia. Titres may persist as long as 1–5 years. Thus a test is available which has the following utility: (1) as a diagnostic marker specificially for halothane hepatitis *v.* other aetiologies of postoperative liver disease; (2) as a marker to determine safety for subsequent halothane anaesthetics in a particular patient.

Although useful as a diagnostic marker, this assay for a trifluoroacetylated carrier protein antibody does not necessarily dictate that halothane produces a hepatic immunological destruction. Dienstag (1980) pointed out that circulating immune complexes can be found in animals following administration of hepatotoxins with basic mechanisms of action outside the purely immunological realm. Popper and Paronetto (1984) have urged caution in determining whether the presence of antibodies is the cause of a tissue injury or the result of a tissue injury.

CURRENT PERSPECTIVES OF HALOTHANE HEPATITIS

Although more and more insights to the problem of halothane hepatitis have been gathered in the past few years, the issue is by no means resolved. There is some speculation that actually two types of hepatic reactions to halothane could exist. The first adverse reaction is rather common and involves quantitative enhancement of the reductive biotransformation of halothane by a variety of factors such as obesity, decreased hepatic blood flow as a result of the anaesthetic, retractors, packs, specific genetic amplification of the reductive pathway, interplay of various inducing drugs and environmental chemicals, etc. Net result is a purely biochemical insult to the liver resulting from reactive intermediates produced by the reductive biotransformation pathway of halothane. The onset of noticeable liver damage is rapid (1–3 days), but remains mild and does not progress to unrelenting severe hepatic necrosis. The second type of reaction postulated is the severe form of liver necrosis usually associated with halothane. It is rare. The basic event is again biotransformation, but the biotransformation leads to conjugation of an intermediate with liver macromolecules, which in turn produces a hapten. Progressive and frequently fatal hepatotoxicity then follows. This reaction is slower to develop than the first, perhaps requiring 6–14 days to become clinically manifest. This is the reaction which can be detected by the circulating antibody. Only through further investigations will these hypotheses be proven or disproven.

Unfortunately, clinical guidelines to avoid this severe complication are still not clear. There seem to be minimal problems in children with repeat halothane exposures, but in adults care should be taken and other anaesthetics considered for frequent anaesthesia. Certainly an unexplained bout of jaundice following a halothane anaesthetic should contraindicate future use of the drug in all but extreme circumstances.

ENFLURANE, ISOFLURANE AND HEPATOTOXICITY

Enflurane is biotransformed to a far less extent than halothane: 2 *v.* 18% of the drug absorbed. Since biotransformation has been frequently associated with viscerotoxicity with other earlier anaesthetics, the potential hazard with enflurane would theoretically be less than that with halothane. Does decreased degree of biotransformation actually produce a safer drug? It is of interest that this seems to be the case. Within 4 years following introduction of halothane there were published at least 350 reported cases of unexplained postoperative jaundice attributed to the anaesthetic. Eight years following the introduction of enflurane to the U.S. market, Lewis and colleagues (1983) published a series of 24 cases they surveyed as "possibly" associated with enflurane. Eger and colleagues (1986) evaluated 88 cases attributed to enflurane anaesthesia and found only 15 of them "possible". Even this "possible" group presented no consistent pathology within the cases. Over 20000000 enflurane anaesthetics had been administered by this time, and the cause–effect relationship of most of the cases was weak at best. Even if true, this indicates a remarkable safety record, with an incidence of less than one case of putative "enflurane hepatitis" per 800000 administrations. This is even less than the spontaneous attack rate of viral hepatitis. Thus this anaesthetic seems safe from a hepatotoxic point of view. In light of present knowledge there would seem to be no contraindication to its use for subsequent anaesthesia. At this time, there have been no case reports of hepatotoxicity attributable to isoflurane and it can probably be safely readministered at fairly closely spaced intervals. Time will determine if this admonition will remain immutable.

It is quite possible a significant lesson has been learned throughout this maze of anaesthetic biotransformation effects: lessened degrees of biotransformation result in decreased viscerotoxicity.

BIOTRANSFORMATION AND NEPHROTOXICITY

The relationship between biotransformation of halogenated anaesthetics to free inorganic fluoride and nephrotoxicity is now an accepted fact. Taves and colleagues (1970) were the first group to link biotransformation of methoxyflurane to fluoride ion and renal damage (high output renal failure). Mazze, Shue and Jackson (1971) can be credited with establishing the cause and effect relationship of methoxyflurane nephrotoxicity to free fluoride ion. Factors such as total dose of anaesthetic, enzyme induction and obesity were proven to enhance biotransformation and hence to worsen renal dysfunction. The possibility that other anaesthetics may be biotransformed to free fluoride in sufficient degree to attain the nephrotoxic plasma concentration of 50–60 μmol litre^{-1} have been examined. Even in the massively obese patient halothane does not produce plasma fluoride ion above 10 μmol litre^{-1}, far lower than the concentrations required to produce subclinical nephrotoxicity (Young et al., 1975). Thus halothane can be exonerated under all circumstances from nephrotoxic potential attributable to biotransformation to free fluoride ion. Because of lack of biotransformation potential, the same can be stated for isoflurane. Enflurane on the other hand, may display renal toxicity under very specific circumstances. Severely obese individuals do show increases in plasma fluoride concentration following prolonged enflurane anaesthesia (Vaughan, 1982). Plasma concentrations of fluoride ion as great as 50 μmol litre^{-1} have been detected in individual obese patients. Thus it is probably good practice to avoid enflurane for prolonged anaesthesia in obese patients. Another biotransformation interaction with enflurane has to do with the antitubercular drug, isoniazid. Isoniazid specifically induces biotransformation of enflurane to fluoride ion (Mazze, Woodruff and Heerdt, 1982). Thus a patient receiving isoniazid is precluded from use of enflurane.

MISCELLANEOUS ADVERSE TOXIC REACTIONS ASCRIBED TO VOLATILE ANAESTHETICS

Certain toxic events have, at one time or other, been attributed to the volatile inhalation anaesthetics. These include central and peripheral nervous system toxicity, immunological toxicity and teratogenic potential. Enflurane, alone amongst the clinically used halogenated drugs, has a direct central nervous system toxicity—convulsions—in high doses concomitant with hypocarbia. This event, while consternating, is not followed by a sustained CNS toxicity. Thus it probably represents no real problem, particularly since it can so easily be avoided. Interestingly, halothane has the potential to produce delayed effects on the CNS, again by means of its biotransformation. It has been demonstrated that the free bromide ion released during oxidative biotransformation of halothane can approach soporific concentrations of this halogen (Tinker, Gandolfi and Van Dyke, 1976). It has been concluded that the result of such biotransformation would not produce any permanent effect, but could perhaps be implicated as a factor in prolonged awakening in older patients following long procedures in which halothane was used. Bromide ion is cleared very slowly by the kidneys, with a half-life exceeding 9 days. Biochemical CNS toxicity produced by halogenated anaesthetics, except for this fugacious effect, probably does not exist. Peripheral neurotoxicity has been attributed to nitrous oxide, but not to volatile anaesthetics.

Immune toxicity may exist to a certain extent following anaesthesia with these drugs, but the effect is again quite short lived, not well documented, and even if it exists may not be of clinical importance. No permanent impairment of immunological integrity has been demonstrated with volatile anaesthetics (Cascorbi and Redford, 1983). Acutely with high blood concentrations, white cell competence is impaired by anaesthetics, a not surprising finding. However this impairment is quickly dissipated as the concentration of anaesthetics decreases.

Reproductive toxicity does not seem to occur consistently in animal studies with relevant concentrations of volatile anaesthetics. Although there have been implications of teratogenic and abortifacient potential of the halogenated anaesthetics, proof of the matter is extremely weak. In fact Ferstanding (1978) has reviewed the evidence published concerning trace concentrations of inhalation anaesthetics as a potential health hazard, and found it poor.

SUMMARY

The volatile inhalation anaesthetics have been implicated in a variety of adverse viscerotoxic reactions. In general, they have been proven to produce very few non-predicted toxicities. Hepatitis caused by halothane now seems to be the only major problem in this regard with these drugs in current practice. The evidence is convincing that this reaction is based initially on biotransformation. Thus decreases in the amount of biotransformation and lessened production of reactive

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metabolic products would theoretically produce a safer anaesthetic. While not perfect in all circumstances, enflurane and isoflurane come close to achieving the goal of decreased adverse viscerotoxic events.

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TOXICITY OF I.V. ANAESTHETICS

J. W. SEAR

I.v. anaesthesia today originates from the introduction of short acting barbiturates, thiopentone, hexobarbitone and butobarbitone, in the 1930s. The first significant report of toxicity from these agents was the profound hypotension recorded when barbiturates were administered to the hypovolaemic patient. Since then, other drugs have been introduced in an attempt to produce hypnosis without other organ or tissue toxic effects. Several of these drugs (hydroxydione, GR 2/146, propanidid, Althesin and minaxolone) are no longer available for use in clinical practice, as a result of undesirable or adverse effects of the drug or its solvent.

This review will consider the presently available i.v. agents from three aspects: the effects of the drugs on the function of body organs and tissues; the factors that increase and decrease plasma drug concentrations, and so bring about changes in the duration or intensity of drug effect; and the minor or unwanted sequelae following use of these drugs for induction or maintenance of anaesthesia.

EFFECTS ON ORGANS AND TISSUES

Heart

All i.v. hypnotic agents have two main effects on the circulation. First, they act to reduce myocardial contractility and increase venous capacitance; second, the effect of sleep is to reduce vascular resistance. Thus, induction of anaesthesia is associated with a decrease in cardiac output, and a decrease in both systolic and diastolic arterial pressure. The accompanying increase in heart rate is probably related to a release of vagal activity, rather than direct sympathetic nerve stimulation.

Effect of induction of anaesthesia on cardiac performance

In man, thiopentone causes increased myocardial blood flow and increased oxygen consumption as a result of a decrease in coronary vascular resistance (Sonntag et al., 1975). Thiopentone and methohexitone also cause reduced myocardial contractility, an increase in left ventricular end diastolic pressure and a decrease in stroke volume, systemic vascular resistance (SVR) and mean arterial pressure. Following the stimulus of surgery, the SVR increases (Prys-Roberts, Sear et al., 1983). Both drugs appear to have little effect in obtunding the haemodynamic response to laryngoscopy and intubation, when compared with some other agents (for example propofol) (Prys-Roberts, 1984).

Etomidate also causes a decrease in cardiac performance. However, Kettler and colleagues (1974) using a dose of 0.12 mg kg^{-1} min^{-1}, found only minimal changes in heart rate, only minimal coronary vasodilatation, and unaltered myocardial oxygen consumption. In larger doses (0.45 mg kg^{-1}), etomidate caused the expected decrease in cardiac index and systemic arterial pressure (Criado et al., 1980).

The cardiovascular effects of the benzodiazepines, and in particular those of midazolam, when used for induction of anaesthesia in healthy patients, appear comparable to those of thiopentone (Lebowitz et al., 1982b). The addition of nitrous oxide does not affect the haemodynamic effects of midazolam (Samuelson et al., 1981).

In healthy patients, ketamine caused enhanced cardiac contractility (Tweed and Mymin, 1974). When given as a 2-mg kg^{-1} bolus during enflurane or halothane anaesthesia, ketamine caused a rapid and significant increase in SVR, and an associated decrease in cardiac output and arterial pressure (Bidwai et al., 1975).

Effect of infusions of i.v. agents on the heart and circulation

The cardiovascular effects of infusions of hypnotic agents to supplement nitrous oxide in oxygen anaesthesia have been delineated by a series of studies from Prys-Roberts and his colleagues (Prys-Roberts, 1984; Coates et al.,

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TABLE I. *Haemodynamic effects of infusions at 1 × MIR (minimum infusion rate) to supplement 67% nitrous oxide in oxygen. Patients were all premedicated with morphine 0.15 mg kg^{-1}, and underwent peripheral vascular surgery. Results shown as % change from the awake value. SVNS = Spontaneous ventilation in absence of surgery; SVS = spontaneous ventilation during surgery; IPPV = Intermittent positive pressure ventilation with surgery. (Data adapted from Prys-Roberts, Davies et al. (1983), Prys-Roberts, Sear et al. (1983) and Coates et al. (1985))*

	MAP	Cardiac output	Systemic vascular resistance	Heart rate	Arterial $P\text{CO}_2$
Methohexitone					
SVNS	−26	−24	−13	+7	+29
SVS	−15	−26	+5	+11	+35
IPPV	−10	−34	+27	+14	—
Propofol (in Cremophor EL)					
SVNS	−28	−19	−17	−9	+30
SVS	−17	−26	+8	−8	+22
IPPV	−10	−29	+30	−4	—
Propofol (in emulsion)					
SVNS	−39	−30	−14	−20	—
SVS	−17	−30	+17	−17	—
IPPV	−8	−38	+42	−16	—

1985). Of the currently available hypotic agents, they have studied the effects of methohexitone and propofol (table I). In order to allow comparison between agents, Prys-Roberts has made measurements in the awake but premedicated patient, during spontaneous ventilation in the absence of surgery (SVNS), and during spontaneous and controlled ventilation in the presence of surgery (SVS and IPPVS, respectively). The infusion rates used were multiples of the minimum infusion rate (MIR) (Sear and Prys-Roberts, 1979a). Both methohexitone and propofol (in Cremophor EL and in the current lipid emulsion formulation) cause similar cardiovascular and respiratory depression—the magnitude being significantly greater than that found previously with Althesin (Sear and Prys-Roberts, 1979a).

Many of the volatile anaesthetic agents suppress the baroreflex control of heart rate, so allowing a decreased arterial pressure to persist with little change in heart rate. In the only published data investigating the effect of i.v. infusion anaesthesia on baroreflex activity, Jones and Prys-Roberts (1983) and Carter and colleagues (1986) have shown Althesin and methohexitone, at infusion rates up to 2 × MIR, to depress baroreflex control to an extent similar to that obtained with the volatile agents.

Liver

Effects of i.v. agents on liver blood flow

Recent studies in the greyhound by Thomson and colleagues (1986) have shown infusions of thiopentone, Althesin and etomidate to produce dose-related decreases in general cardiovascular indices (mean arterial pressure, cardiac output and systemic vascular resistance). These changes were accompanied by decreases in total liver blood flow. In addition, both Althesin and etomidate, when given at low infusion rates (total steroid 20 µg kg^{-1} min^{-1} and 80 µg kg^{-1} min^{-1}, respectively) produced a significant decrease in hepatic arterial blood flow in the absence of any effect on the systemic circulation. This suggests a local vasoconstrictor effect. A similar observation has been made in patients receiving halothane and methoxyflurane (Libonati et al., 1973; Thulin, Andreen and Irestedt, 1975; Benumof et al., 1976; Hughes, Campbell and Fitch, 1980), as well as with Althesin and ketamine when added to the isolated perfused rat liver (Sear, 1981; J. Sear and P. Davies, unpublished observations).

All three i.v. agents at low infusion rates caused increases in hepatic artery and mesenteric vascular resistance. At higher infusion rates (approximately three times the initial infusion rates), the decreases in liver blood flow were secondary to myocardial depression. Van Lambalgan and colleagues (1982) have described a time-dependent decrease in hepatic artery blood flow during a constant infusion of etomidate 4 mg kg^{-1} h^{-1} to the dog. Again, this was secondary to a progressive decrease in cardiac output as a result of reduced myocardial contractility.

The concept of a reciprocity between the liver blood flow components (hepatic artery and hepatic portal venous flow) has been reported in animals. Thus, an increase in arterial flow occurs in response to decreased portal flow. This was not seen by Thomson and colleagues (1986) during i.v. infusion anaesthesia, and therefore represents the loss of a beneficial response which avoids hepatic hypoxia. Similar loss of reciprocity has been seen during enflurane and halothane anaesthesia, although increasing inspired concentrations of halothane were accompanied by little change in hepatic arterial resistance. Enflurane caused a dose-related decrease in arterial vascular resistance. Hepatic oxygen consumption was unaltered during anaesthesia supplemented by halothane or enflurane, and during infusion of these three i.v. agents. However, all anaesthetics cause a decreased oxygen supply.

Effects of i.v. agents on liver function tests

Several authors have studied the effects of i.v. agents, either as a bolus dose or by continuous infusion, on the routinely measured hepatic function tests. Dundee and colleagues have shown that infusions of Althesin, thiopentone, etomidate, propofol and bolus doses of midazolam have no gross effect on liver enzymes in patients undergoing minor gynaecological surgery (Blunnie et al., 1981; Kawar et al., 1982; Robinson and Patterson, 1985). However, infusions of ketamine to similar patient groups resulted in increases in alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT) 3–4 days after operation (Dundee et al., 1980).

Sear, Prys-Roberts and Dye (1983) and Prys-Roberts, Sear and colleagues (1983) studied the effects of infusions of Althesin, minaxolone, propofol and methohexitone to supplement 67% nitrous oxide in oxygen in patients undergoing major vascular reconstructive surgery. Liver function tests were measured for 7–10 days after operation and comparison made with other patients receiving halothane. There were no significant differences between the groups with respect to aspartate aminotransferase (AST), total lactic dehydrogenase (LDH), GGT or alkaline phosphatase. Isolated increases in enzyme activity above the normal range occurred in all patient groups. Use of the liver specific enzyme, ornithine carbamoyl transpeptidase (OCT) showed no increases beyond the normal range over the 7 days after surgery. The absence of any increase of OCT in patients receiving halothane was in contrast to the results of Brohult (1967) and Thompson and Friday (1978). Estimation of the liver isoenzyme of LDH (LDH_5) showed activities of greater than 16% total activity in one or more postoperative samples in four of six patients receiving methohexitone by infusion (Prys-Roberts, Sear et al., 1983). However, this was not accompanied by significant increases in OCT activity. Thus, it is reasonable to conclude that, *in our study*, continuous infusion of methohexitone (in total dose of 767–1531 mg) to supplement nitrous oxide anaesthesia was not associated with evidence of acute hepatocellular dysfunction. This is contrary to the observations of Bittrich, Kane and Mosher (1963), who administered total drug doses of up to 600 mg of methohexitone. Similarly, Dundee (1955) has shown large doses of thiopentone to cause abnormalities of liver function tests.

Enzyme changes, similar to those reported by Sear, Prys-Roberts and Dye (1983) for propofol, Althesin and minaxolone, were found in patients receiving an infusion of etomidate 10 μg kg^{-1} min^{-1} or halothane to supplement nitrous oxide in oxygen anaesthesia for lumbar spinal laminectomy (Sear et al., 1984).

Viegas and Stoelting (1979) compared the release of LDH_5 in patients undergoing cholecystectomy or abdominal hysterectomy during halothane-, enflurane- or fentanyl-supplemented anaesthesia. The enzyme leakage into the blood was significantly greater in the upper abdominal surgery groups, but there was no difference between the anaesthetic techniques used. This confirms the observation that greater hepatic enzyme leakage occurs during surgery within close proximity of the liver.

Increases in GGT were observed over the first 7 days after operation during halothane and Althesin infusion anaesthesia (Sear, Prys-Roberts and Dye, 1983). Similar changes have been seen by Massarrat and Massarrat (1979) in patients undergoing vaginal hysterectomy under either halothane, neuroleptanaesthesia, or extradural anaesthesia. It is possible either that these changes represent a late hepatic response to factors released through increased tissue necrosis and catabolism following surgery, or that both drugs act as induction agents of microsomal and other enzymes. There is other evidence (Duvaldestin et al., 1981; Nimmo, Thompson and Prescott, 1981) to show that either thiopentone–halothane or neuroleptanaesthesia may cause enzyme induction to occur.

At present, there are no data comparable to the results of Allan and colleagues (1986) that both halothane and enflurane anaesthesia may cause increased plasma concentrations of another liver cytosol enzyme, glutathione s-transferase, (GST). Studies in patients admitted following paracetamol overdose may show marked increases in plasma GST concentrations by 40 h after ingestion, with minimal changes detectable by as early as 4 h (Beckett et al., 1985).

In conclusion, therefore, it appears that single infusions of all the i.v. hypnotic agents (with the possible exceptions of thiopentone and ketamine) cause only minimal alterations in plasma concentrations of the routinely measured liver function tests. There are no data at present on the effects of continuous infusions of hypnotic agents for repeat anaesthesia.

Effects of i.v. anaesthetics on metabolism in isolated liver cells and perfused liver

The studies of Biebuyck, Lund and Krebs (1972) showed the effect of halothane on liver metabolism to be a primary interference with mitochondrial ATP synthesis. Gluconeogenesis (from lactate 10 mmol litre^{-1}) was less affected by the addition of ketamine 365 μmol litre^{-1} than by 2.5% halothane v/v. Strunin (1977) has shown the volatile agents to inhibit the clearance of bromsulphthalein, indicating an alteration of the excretory function of the liver.

Isolated liver cells in suspension or in culture have been used to study the cytotoxic effects of a number of drugs. Of the criteria quoted by Baur, Kasperek and Pfaff (1975) to assess the viability of the cells, the hepatocyte ATP concentration and gluconeogenesis from alanine appear to be the most sensitive. In addition, leakage of LDH can be easily measured.

Table II shows the concentrations of Althesin, ketamine, minaxolone, propofol and methohexitone required to inhibit gluconeogensis from alanine 10 mmol litre^{-1}, in addition to the concentrations of some of the agents needed to cause 50% LDH leakage. The former appears to be the more sensitive criterion of cell damage (Sear and McGivan, 1979).

There are few other data on the effects of i.v. agents on intermediary metabolism in man or the experimental animal. Dye and Taberner (1975) investigated the effects of Althesin, pentobarbitone, thiopentone, methohexitone and ketamine on glutamic acid decarboxylase (GAD) and GABA amino-transferase in mouse brain tissue. Ketamine produced competitive inhibition of GAD at concentrations greater than 8 mmol litre^{-1}, as did alphaxalone at greater than 1.36 mmol litre^{-1}. The barbiturates caused non-competitive inhibition, but only at high concentrations ($>$ 20 mmol litre^{-1}). None of the agents investigated had any effect on GABA aminotransferase activity. Using brain homogenates and crude mitochondrial fractions, Dye and Taberner showed that single doses of Althesin 16 mg kg^{-1} i.p. inhibit only homogenate cytochrome oxidase—not the mitochondrial enzyme. Thus, the effect of the anaesthetic was probably related to change in cytosol redox coupled reactions rather than an effect on the mitochondrial enzymes.

Although a number of general anaesthetics have been shown to inhibit mitochondrial respiration *in vitro* (Cohen, 1973), there is no evidence of changes *in vivo* in brain ATP concentrations

TABLE II. *Concentration of i.v. anaesthetic agents needed to 50% inhibit gluconeogenesis from alanine 10 mmol litre^{-1} and cause leakage of 50% total cellular lactic dehydrogenase from hepatocytes prepared from starved male rats. *During constant rate infusion to supplement 67% nitrous oxide.* n = *Number of cell preparations. (Adapted from Sear and McGivan (1979))*

Anaesthetic agent	*n*	50% Inhibition of gluconeogenesis (μmol litre^{-1})	50% Leakage of LDH (μmol litre^{-1})	Anaesthetic concn in plasma* (μmol litre^{-1})
Alphaxalone	8	443	303	4.5
Minaxolone	4	286	1785	1.6
Methohexitone	2	375	—	10.6
Ketamine	3	458	—	7.5
Propofol	2	881	—	6.6

(Nilsson and Siesjo, 1971; Fink and Haschke, 1973).

In vitro studies using rabbit brain and liver mitochondria (Smith, Sweetman and Esmail, 1974) have shown Althesin to have two separate dose-related effects on ATP synthesis: at low concentrations (70 µmol litre^{-1}), the drug-inhibited electron transport between NADH and cytochrome b; at higher concentrations (333 µmol litre^{-1}), uncoupling of oxidative phosphorylation occurred. Similar effects in uncoupling oxidative phosphorylation have been demonstrated for the barbiturates. Benzi and colleagues (1980) confirmed the findings of Dye and Taberner (1975) that Althesin reduced cytochrome oxidase activity. They also showed, using rat brain preparations, that it has no actions on other enzymes of the Krebs cycle, pentose phosphate or glycolytic pathways. Similar experiments using pentobarbitone 100 mg kg^{-1} i.p. revealed a decrease in both cytochrome oxidase and malate dehydrogenase activity (Benzi et al., 1979). This supports previous observations that the barbiturates cause mitochondrial accumulation of malate, increased concentrations of glutamine, but unchanged concentrations of citrate and glutamate. Sweetman and Esmail (1982) have demonstrated a further effect of the steroid anaesthetic agents on mitochondrial function. Alphaxalone 69–260 µmol litre^{-1} *in vitro* and Althesin 12 mg kg^{-1} i.v. inhibited the mitochondrial uptake of $^{45}\text{Ca}^{2+}$, the ED_{50} dose being alphaxalone 130 µmol litre^{-1}. Normally, the mitochondrion sequesters calcium from the cytosol at the expense of ATP utilization. This process can be inhibited by uncoupling agents such as 2,4-dinitrophenol. Thus, although there was no apparent effect of i.v. steroid agents on ATP synthesis *in vivo*, alphaxalone significantly inhibited calcium uptake into the mitochondrion. Althesin, as well as hexobarbitone 90 mg kg^{-1} i.p., affected the distribution of calcium within the rat brain. In the presence of these anaesthetics, a greater percentage of labelled calcium passed to the post-mitochondrial supernatant, rather than binding within the mitochondrial fraction. The increased concentrations of calcium in the cytosol during anaesthesia may interfere with calcium dependent activities (transmitter release and membrane excitability).

TABLE III. *Effect of i.v. anaesthetic agents on hepatic Δ-aminolaevulinate (ALA) synthase activity using rat liver homogenate (mean ± SEM). *$P < 0.01$ compared with the control rate in absence of any anaesthetic agent. (Adapted from Parikh and Moore (1978) with permission of the authors and the publishers of the* British Journal of Anaesthesia)

Agent	ALA activity (nmol g^{-1} h^{-1})
Control	37.0 (15.2)
Thiopentone	79.1 (20.0)*
Etomidate	118.6 (29.2)*
Methohexitone	89.6 (28.3)*
Althesin	96.8 (22.6)*
Pentazocine	53.9 (13.0)*
Propanidid	39.6 (19.8)
Ketamine	42.8 (16.6)
Diazepam	43.4 (14.1)
Pethidine	37.3 (18.6)
Morphine	39.2 (9.8)
Nitrous oxide	40.8 (26.4)

Effects on hepatic porphyrin metabolism

Drugs are among the commonest of the exogenous factors that precipitate attacks of acute porphyria and, of these, Eales (1971) has shown the barbiturates to be the most important of the i.v. agents. The response of a susceptible individual to any porphyrogenic drug is unpredictable, but subclinical doses have been reported to elicit severe and even fatal episodes. Parikh and Moore (1978) studied the effects of some of the i.v. anaesthetic agents on hepatic Δ-aminolaevulinate (ALA) synthase activity in rat liver homogenate. Drugs were given daily by the i.p. route over a 4-day period; the animals were then sacrificed and liver enzyme activity assayed. Table III gives data for many of the commonly used i.v. agents. A positive stimulant effect is seen as an increase in liver homogenate enzyme activity. Of those drugs tested, thiopentone, etomidate, methohexitone and pentazocine increase ALA synthase activity.

Using a different model (namely the DDC-primed rat), Blekkenhorst and colleagues (1980) have failed to show any increase in ALA synthase activity following a single i.p. dose of etomidate. More recently, Harrison, Moore and Meissner (1985) have investigated the porphyrinogenicity of etomidate and ketamine when given by infusion to the DDC-primed rat. Ketamine showed no effect on ALA synthase, but etomidate caused a significant (47%) increase in enzyme activity and an associated increase in coproporphyrin and protoporphyrin in the liver homogenate. However, ketamine has been shown to induce ALA synthase formation in the chick embryo liver (Kostrzewska, Gregor and Lipinska, 1978).

It is thought that the basic problem in porphyria is one or more enzyme defects along the biosynthesis pathway of haem. The only exception to this may be variegate porphyria. The incidence of attacks of porphyria varies with location. Thus, in South Africa, the incidence in whites and coloureds is about 1/1000; while in Northern Ireland, Western Australia and Seattle, the figures are about 1/80000, 1/30000 and 1/7000, respectively (G. Harrison, personal communication). Of the 145 episodes seen at the Groote Schur Hospital, Cape Town from 1951 to 1971, 31 were precipitated by thiopentone, and two of these resulted in death (Whitwam, 1984).

Kidney

Induction of anaesthesia causes significant changes in renal haemodynamics, and water and electrolyte excretion. Renal blood flow normally shows autoregulation over a wide systemic arterial pressure range. This regulation was originally thought to be vascular in origin, but more recent data have suggested that the mechanism brings about the delivery of a constant quantity of sodium to the tubules by variations of the glomerular filtration rate (GFR). There are also neurogenic controls of the renal vasculature. Increased neuronal firing during exercise results in a reduced renal perfusion, but unchanged glomerular filtration. Both adrenaline and noradrenaline act to reduce renal blood flow and the effects of these catecholamines and angiotensin II may be further modulated by the renal vasodilator properties of prostaglandins E and A. The increased concentrations of ADH, seen in response to stress of any kind, act to regulate medullary blood flow by causing vasoconstriction of the efferent arterioles of the juxtaglomerular region. This enhances medullary hypertonicity, and hence water reabsorption.

General anaesthesia causes a decrease of both renal blood flow and GFR. Studies with the i.v. agents (mainly thiopentone) in volunteers and patients show these changes to be accompanied by a decreased urinary flow, and decreased sodium excretion (Habif et al., 1955; Gorman and Craythorne, 1966; Deutsch et al., 1969). As a result, the urine: plasma osmolar ratio is increased. The mechanisms by which i.v. agents affect salt and water excretion include changes in systemic haemodynamics, liberation of ADH and a possible aldosterone effect on the distal convoluted tubule following activation of the renin–angiotensin system.

Thiopentone causes an increase in renal vascular resistance (RVR) (Deutsch et al., 1969), so that blood is effectively shunted away from the kidney to compensate for the hypotension seen as a result of myocardial depression and peripheral vasodilatation. In a comparative study in man investigating the renal effects of thiopentone and midazolam (Lebowitz et al., 1982a), the benzodiazepine caused a greater reduction in renal blood flow and GFR—although the increase in RVR was numerically smaller than that seen with thiopentone. In the normovolaemic dog, diazepam 2 mg kg^{-1} caused significant reduction in RBF by an 8–12% increase in RVR, while ketamine 5 mg kg^{-1} increased renal perfusion. Ketamine had no significant effect on RVR (Priano, 1982). High dose fentanyl given to the non-anaesthetized dog increased systemic arterial pressure and cardiac output, but did not affect renal blood flow (as a result of an increase in RVR) (Priano, 1983). In contrast, Bidwai and colleagues (1976) have demonstrated a diminished urine output and free water clearance, and increased urinary osmolarity in the anaesthetized dog receiving fentanyl. This was probably the result of an increased secretion of ADH. These changes are also in contrast to the renal vasodilatation seen with morphine and pethidine (Priano and Vatner, 1981a, b).

The adverse effect of i.v. drugs on the kidney are similar to those described for the volatile agents. There are no data at present on the effects following i.v. infusions of the hypnotic agents; nor are there data on whether or not dose-related changes are seen—as with the effects of these agents on the heart and peripheral vascular system (Prys-Roberts, 1984).

Blood

Effects of i.v. hypnotic agents on blood biochemistry

Bond (1969) demonstrated a 5% decrease in the blood haemoglobin concentration within 16–30 min of induction of anaesthesia in patients receiving thiopentone. Similar changes have been reported by Lacoumenta and colleagues (1984) and Sear, Uppington and Kay (1985) in patients receiving ketamine, and Althesin or propofol, respectively, for induction of anaesthesia. The exact mechanism for this haemodilution remains uncertain, but it may represent either an alteration in the relationship between the capillary perfusion

TABLE IV. *Plasma sodium and urea concentrations (mean ± SEM) in five samples taken after abdominal hysterectomy in patients receiving thiopentone–halothane* (n = 9), *etomidate–halothane* (n = 5), *or an infusion of etomidate (10 µg kg^{-1} min^{-1})* (n = 6) *to supplement 67% nitrous oxide in oxygen. Sample timings: 1 = before induction; 2 = at end of surgery (approximately 90 min after induction); 3 = 4 h after induction; 4 = 10 h after induction; 5 = 24 h after induction.*
*P < *0.01 compared with the pre-induction value*

	Sodium (mmol litre^{-1})					Urea (mmol litre^{-1})				
Anaesthetic	1	2	3	4	5	1	2	3	4	5
Thiopentone–halothane	141.2 (3.6)	139.7 (4.4)	143.9 (5.0)	143.2 (5.8)	136.6 (3.0)	3.67 (0.38)	3.74 (0.37)	3.82 (0.38)	3.89 (0.53)	3.09 (0.43)
Etomidate–halothane	136.8 (1.4)	135.8 (0.6)	141.4 (3.9)	134.8 (1.1)	140.0 (2.4)	3.62 (0.30)	3.84 (0.31)	3.92 (0.24)	3.76 (0.21)	2.44* (0.41)
Etomidate infusion	142.3 (7.1)	143.4 (7.1)	147.0 (4.2)	139.5 (9.3)	144.5 (6.9)	3.52 (0.31)	3.42 (0.44)	3.88 (0.45)	3.37 (0.54)	2.10* (0.18)

pressure and plasma colloid oncotic pressure, or a redistribution of blood rich in cells, and blood poor in cells. Studies on the effects of bolus doses or infusions of i.v. agents generally show no change in concentrations of plasma electrolytes or urea. However, in patients undergoing abdominal hysterectomy under general anaesthesia (with an infusion of etomidate 10 µg kg^{-1} min^{-1} or halothane to supplement nitrous oxide in oxygen), we have recently demonstrated a greater haemodilution at 24 h in those patients receiving etomidate (table IV).

Use of hypnotic drugs in the intensive care unit for sedation for controlled ventilation allows study of the safety of large doses of the drugs. As already discussed, thiopentone by infusion may result in hepatotoxicity, as assessed by BSP retention. Gibbs and colleagues (1984) studied the effects of long-term continuous infusion of Althesin on biochemical and haematological parameters in 12 neurosurgical patients. The average duration of infusion was 7.8 days, with a mean total dose of 1823 ml (21.9 g of total steroid). The main biochemical changes after infusion were a decrease in serum albumin concentration, an increase in triglycerides and an associated decrease in high density plasma lipids. Haematological changes were also seen, with a 20% decrease in haemoglobin concentration and significant increases in plasma fibrinogen and viscosity. Cellular morphology on a blood film showed distortion of the contour of red cells, and an irregular distribution of white cells and platelets. The aetiology of these findings remains uncertain.

Other authors have described further biochemical changes associated with the prolonged infusion of Cremophor EL (the solvent for Althesin) (Bagnarello et al., 1977; Forrest, Watresiewicz and Moore, 1977). These include an abnormal electrophoretic pre-beta band, and an absence or marked reduction of the alpha band (mainly high density lipids). There have also been reports of abnormal liver function during infusion of Althesin (Ramsay et al., 1974; Stewart, Dobb and Craig, 1983; Lawler, McHutchon and Bamber, 1983).

The other hypnotic agents do not appear to cause significant effects on blood biochemistry when given by infusion—with the exception of etomidate (see later) and chlormethiazole, which may increase cellular fragility if given by prolonged infusion.

Effects of i.v. agents on blood coagulation and fibrinolysis

Gaszynski and colleagues (1974) demonstrated that both single dose and repeated increments of Althesin caused changes in the blood coagulation system. There was an increase in clot retraction and in the platelet count, as well as activation of the formation of thromboplastins. More recent studies comparing the effect of Althesin and propofol on the coagulation system have shown no significant changes in the platelet count, or in several measured indices of coagulation (prothrombin ratio, PTT, thrombin time) (Sear, Uppington and Kay, 1985).

Further studies with propofol must involve investigation of the effect of infusions of the agent on blood coagulation, as Amris, Brockner and Larsen (1964) showed Intralipid infusion to affect coagulation, while Reid and Ingram (1967) demonstrated fat emulsions to possess weak antiplatelet activities.

There are few data on the effects of anaesthesia on blood fibrinolysis, although Oyama and colleagues (1967) showed the use of halothane to be associated with reduced fibrinolytic activation. Simpson and colleagues (1982) confirmed this effect, and found there to be enhanced fibrinolytic activation produced by trichloroethylene and extradural anaesthesia. Fentanyl, in doses of 2 μg kg^{-1} to supplement nitrous oxide in oxygen, was accompanied by increased fibrinolysis, although the onset was delayed by larger doses (10 μg kg^{-1}).

No differences were seen between volatile agents, extradural anaesthesia or fentanyl with respect to the increase in fibrin degradation products (FDP).

In a more recent study investigating the effects of incremental doses of propofol or Althesin to supplement nitrous oxide in oxygen for body surface surgery, Sear, Uppington and Kay (1985) found no difference in fibrinogen titre or FDP between a pre-induction sample and one taken 30 min after the onset of anaesthesia (about 15–20 min after the start of surgery).

Adrenal Cortex

All surgical procedures cause the initiation of endocrine responses, resulting in the mobilization of substrates, protein catabolism with the development of a negative nitrogen balance, and the retention of salt and water. Clarke, Johnston and Sheridan (1970) showed the magnitude of this neuroendocrine response to be proportional to the severity of the surgical procedure.

The plasma cortisol concentration increases rapidly after the onset of surgery, and may remain increased for up to 24 h after surgery (Moore et al., 1985). The stimulus for this increased cortisol production is an increased secretion of ACTH (Oyama and Takiguchi, 1970). However, Thoren (1974) has shown the ACTH concentration to be far in excess of that needed to produce maximal adrenocortical response. In addition, the normal homeostatic feed-back mechanism between the pituitary and the adrenal gland appears to be inhibited as both ACTH and cortisol concentrations increase simultaneously. Johnston (1964) has shown that the urinary excretion of cortisol metabolites, 17-ketogenic steroids, remained increased for 3–4 days after surgery, and that this increase persisted longer in the presence of surgical complications.

There are few studies investigating the influence of anaesthetic agents in the absence of surgery. Engelhardt and colleagues (1984) studied the influence of thiopentone 4 mg/kg body weight and etomidate 0.3 mg kg^{-1} on plasma ACTH and serum cortisol concentrations in groups of male volunteers over a 5-h period. Thiopentone caused a maximal decrease of about 30% in the cortisol concentration, while that in the etomidate group decreased by a maximum 62%. Neither group showed a return to pre-anaesthetic values by 300 min. The plasma ACTH concentration following thiopentone showed an initial decrease, but then returned to basal values for the remainder of the study period. By contrast, the etomidate group showed a 100% increase in ACTH concentrations over the 300-min study period.

In the rat, Preziosi (1983) demonstrated etomidate 20 μmol kg^{-1} to obtund the response, measured as plasma corticosterone, to synthetic ACTH 700 mu. kg^{-1}. This supported a central mechanism of action of the drug. Furthermore, Preziosi, Cerrito and Vacca (1983) showed etomidate to inhibit prolactin release in the rat via a non-dopaminergic mechanism. Neither Althesin 0.075 ml kg^{-1} nor ketamine 2 mg kg^{-1} inhibited the adrenocortical response to surgery, although inhibition was seen during deep anaesthesia with Althesin 1.75 ml kg^{-1} (Nistico et al., 1978). More recently, Blackburn and colleagues (1985) have compared the effects of infusions of etomidate, methohexitone and propofol in the female rat. In animals receiving methohexitone, anaesthesia was associated with increased serum corticosterone concentrations. Following Synacthen 25 μg, significant increases in corticosterone occurred only in those animals receiving methohexitone or propofol.

Various groups have investigated the effects of i.v. agents on cortisol synthesis using isolated bovine or guineapig adrenal cells (Kenyon, McNeill and Fraser, 1985; Lambert, Mitchell and Robertson, 1985). Cortisol synthesis is stimulated by the addition of ACTH 10^{-9} mol $litre^{-1}$ to the incubation medium and the concentration of anaesthetic agent required to inhibit 50% of the ACTH-stimulated cortisol synthesis is determined. Table V shows the ED_{50} values for thiopentone, propofol and etomidate, together with the estimated plasma drug concentration in man 1 min after induction of anaesthesia. From these data, the extent of inhibition of cortisol synthesis, by the estimated 1-min plasma concentration, will be approximately 10%, 40% and

TABLE V. *Concentrations of thiopentone, etomidate and propofol associated with 50% inhibition of cortisol synthesis following ACTH stimulation of isolated bovine or guineapig adrenal gland cells in suspension*

	Bovine cells (Kenyon, McNeill and Fraser, 1985) (mol litre^{-1})	Guineapig cells (Lambert, Mitchell and Robertson, 1985) (mol litre^{-1})	Induction dose in man (mg kg^{-1})	Plasma concn 1 min after induc. dose (mol litre^{-1})
Thiopentone	3×10^{-5}	1.6×10^{-4}	5.0	1.1×10^{-4}
Etomidate	4.6×10^{-7}	1.0×10^{-7}	0.3	$4.6\text{–}5.7 \times 10^{-6}$
Propofol	1.1×10^{-4}	1.7×10^{-4}	2.0	$3.4\text{–}6.9 \times 10^{-6}$

100%, respectively for propofol, thiopentone and etomidate.

Interest in the influence of i.v. agents on these normal neuroendocrine responses to surgery and trauma have been heightened by the studies of Watt and Ledingham (1984). They have suggested that use of etomidate in the I.T.U. to provide sedation in the multiply injured patient may be associated with an increase in mortality—secondarily to this inhibition of cortisol synthesis. Furthermore, Miranda and Stoutenbeek (1983) have reported unaltered mortality in patients sedated with etomidate by infusion, *but* given prophylactic steroids on admission to the I.T.U.

Numerous papers have delineated the site of action of etomidate on the steroid biosynthetic pathways in man, and the experimental animal. In man, bolus doses (0.3 mg kg^{-1}) and infusions up to a total dose of etomidate 1.2 mg kg^{-1} cause inhibition of the 11-beta hydroxylase enzyme. This will result in decreased synthesis of cortisol, and increased concentrations of the precursor, 11-deoxycortisol (Fry and Griffiths, 1984; Moore et al., 1985). There is also inhibition of the conversion of 11-deoxycorticosterone (DOC) to corticosterone (Duthie, Fraser and Nimmo, 1985; Sear, Atherden and Edwards, 1985), with decreased plasma concentrations of aldosterone (Fragen et al., 1984; Wagner and White, 1984; Moore et al., 1985). However, Sear, Atherden and Edwards (1985) have shown the increase in DOC to be significantly greater at 4 h after the onset of surgery in patients receiving a bolus dose of etomidate, when compared with those receiving an infusion of the drug. This suggests a second, dose-related inhibition of DOC through an early pathway effect at etomidate doses in excess of 1.2 mg kg^{-1}. Further evidence for a second inhibitory site between cholesterol and progesterone has been obtained by determination of the plasma progesterone concentration (table VI). In 15 patients undergoing abdominal hysterectomy, cortisol and progesterone concentrations were measured before induction, at the end of surgery and at 4 h, 10 h and 24 h after induction. Anaesthesia was induced with thiopentone or etomidate, and maintained with nitrous oxide in oxygen supplemented by halothane or an etomidate infusion. Although there was a dose-related inhibition of cortisol secretion, the effect on the synthesis of progesterone appears to be an all-or-none effect related to the use of etomidate.

All studies in man, unlike those in animals, have

TABLE VI. *Plasma cortisol (nmol litre^{-1}) and progesterone (nmol litre^{-1}) concentrations (mean ± SEM) in five samples taken after abdominal hysterectomy in patients receiving thiopentone–halothane (n = 5); etomidate–halothane (n = 5) or an infusion of etomidate (n = 6) to supplement 67% nitrous oxide in oxygen. Sample timings: 1 = Before induction; 2 = at end of surgery (approximately 90 min after induction); 3 = 4 h after induction; 4 = 10 h after induction; 5 = 24 h after induction.* *$P < 0.01$ *compared with pre-induction value*

	Cortisol					Progesterone				
	1	2	3	4	5	1	2	3	4	5
Thiopentone–halothane	275 (54)	840* (55)	1120* (117)	1033* (108)	480* (100)	1.54 (0.64)	3.94* (1.68)	5.16* (2.09)	4.93* (1.27)	1.74 (0.33)
Etomidate–halothane	444 (60)	289* (8)	356 (28)	796* (63)	434 (43)	3.57 (2.14)	3.13 (1.45)	5.28 (1.53)	8.66* (2.04)	2.78 (0.55)
Etomidate infusion	364 (65)	277* (51)	320 (36)	586* (70)	718* (137)	5.57 (1.35)	8.34 (3.29)	10.19 (3.53)	13.96* (3.91)	6.52 (1.55)

shown no effect of etomidate on the pituitary secretion of ACTH (Fragen et al., 1984; Wagner and White, 1984; Duthie, Fraser and Nimmo, 1985; Moore et al., 1985).

There is no evidence that other i.v. agents have any effect on the normal neuroendocrine response to surgery (Lacoumenta et al., 1984; Kay et al., 1985; Mehta et al., 1985).

FACTORS AFFECTING THE PLASMA DRUG CONCENTRATION

The disposition and metabolism of i.v. hypnotic agents may be affected by several clearly defined factors. Alteration in drug kinetics of the single dose of a drug will alter the drug concentration–time profile, and may result in either prolongation or shortening of the duration of effect of the agent, together with alteration in the intensity of the drug effect. For drugs given by continuous infusion, alteration in kinetics will lead to altered steady state drug concentrations, and hence variation in the intensity of drug effect. Thus, in cirrhotic patients receiving Althesin by infusion to supplement nitrous oxide in oxygen anaesthesia (Sear and Prys-Roberts, 1979b), there was a significantly lower plasma drug concentration for comparable infusion rates compared with healthy patients. These effects may be explained on the basis of changes in drug binding, and hence drug disposition. As a result, adequate anaesthesia was obtained at lower *total drug concentrations* in the cirrhotic patient compared with normal healthy individuals.

Factors Affecting Drug Kinetics

Liver blood flow

Hepatic blood flow, intrinsic clearance and the total drug concentration–time profile are interrelated. Intrinsic clearance is an index of the maximum possible clearance rate under conditions where blood flow to the liver is not rate-limiting. If the intrinsic clearance of a drug with a low extraction ratio (ER) is doubled (as may occur during enzyme induction), the main effect is an increase in the efficiency of hepatic extraction (from, say, 0.1 to 0.2). However, for drugs with a high ER, a doubling of the intrinsic clearance will result in only a small increase in the efficacy of hepatic clearance (from, say, 0.9 to 0.95). Under these two differing conditions, and assuming a liver blood flow of 1.5 litre min^{-1}, the systemic clearance in the first case will increase from 0.15 to 0.30 litre min^{-1} while, in the second, there will be only a small increase from 1.35 to 1.42 litre min^{-1}. By contrast, the effects of altering hepatic blood flow will be greatest in the systemic clearance of drugs with a high ER (Wilkinson and Shand, 1975).

Protein binding

In the body, an equilibrium exists between drug bound to plasma and other tissue proteins and free or unbound drug. The extent of plasma protein binding will affect both the distribution and elimination of the drug. The free drug fraction exerts its pharmacological effects, and only this fraction is available for biodegradation by the microsomal mixed function oxidases of the liver and other metabolic organs.

A change in plasma protein or tissue protein binding, through either drug interaction or disease process, may significantly alter the volume of distribution of the drug. Similarly, changes in plasma protein binding may influence the distribution of drug within the intravascular space, resulting in changes in the blood:plasma ratio. Changes in the concentration of the alpha-1-acid glycoproteins (α1 AG) (acute phase reactant proteins) may also lead to alterations in protein binding. Such increases in α1 AG occur in chronic inflammatory diseases, while decreases are seen in the neonate. In general, alterations in protein binding, and therefore of the percent free fraction, are only of importance for drugs that are highly protein-bound.

Extraction ratio

When drug passes through an organ or tissue where metabolism occurs, the inflow concentration will exceed that in the effluent. The extraction ratio (ER) may be defined as:

$$\text{ER} = \frac{C_{\text{in}} - C_{\text{out}}}{C_{\text{in}}} \times \frac{1}{\text{Flow}}$$

Drugs may broadly be allocated into two groups, based upon the avidity of their extraction as they pass through the liver. High clearance drugs have an extraction ratio > 0.7 (flow-limited), while low clearance (capacity-limited) drugs have an ER < 0.3. For high ER drugs, clearance will be affected by alterations in liver blood flow, while the low ER drugs will show changes in clearance following increases or decreases in microsomal enzyme activity (table VII).

TABLE VII. *Effect of increased hepatic blood flow and enzyme induction on the disposition of high and low extraction ratio compounds*

	Low (< 0.3)	High (> 0.7)
Effect of increased liver blood flow		
Plasma drug concentrations	No change	Decreased
Systemic clearance	No change	Increased
Elimination half-life	No change	Decreased
Intensity of effect	No change	May be decreased
Duration of effect	No change	Shortened
Effect of increased enzyme activity		
Plasma drug concentrations	Decreased	No change
Systemic clearance	Increased	No change
Elimination half-life	Decreased	No change
Intensity of effect	May be decreased	No change
Duration of effect	May be shortened	No change

Drug Metabolism during Anaesthesia, and in Disease States

What factors may, therefore, alter the kinetics of the i.v. hypnotic agents, and result in changes in plasma drug concentrations? Most of the i.v. agents (with the exception of thiopentone) are high ER drugs (ER > 0.5) with clearance values between 500 and 1800 ml min^{-1} in the anaesthetized healthy patient. Consequently, drug kinetics will be mainly affected by changes in liver blood flow (table VIII).

Physiological factors

Prys-Roberts and colleagues (1967) demonstrated that cardiac output decreases during intermittent positive pressure ventilation (IPPV). Because hepatic blood flow is not subject to autoregulation as is seen in the kidney, flow to the liver decreases during anaesthesia *per se*, and by a greater amount during IPPV. Thus, Sear and Prys-Roberts (1979a, b) found the plasma alphaxalone concentration at $1 \times$ MIR(13.5 μg kg^{-1} min^{-1}) to be 1.39 μg ml^{-1} in the spontaneously breathing subject, and 1.89 μg ml^{-1} ($P < 0.01$) in the ventilated patient.

The institution of excessive controlled ventilation with the development of hypocapnia, will lead to decreases in both hepatic arterial and hepatic portal venous flow. The restoration of normal carbon dioxide tensions whilst still maintaining hyperventilation results in a return of portal flow to control values, but a further decrease in hepatic artery flow (Hughes et al., 1979).

Hypercapnia causes splanchnic vasoconstriction during the administration of most volatile agents, with the possible exception of halothane, which appears to suppress the constrictor reflex. Thus, the clearance of flow-limited drugs should

TABLE VIII. *Factors affecting liver blood flow in man. (Adapted from Nies, Shand and Wilkinson (1976) with permission of the authors and the publishers of* Clinical Pharmacokinetics)

	Increased	Decreased
Physiological	Supine posture Food intake, digestion	Upright posture Thermal stress Exercise Volume depletion
Pharmacological	Glucagon Isoprenaline Phenobarbitone Calcium channel blockers (?Diltiazem)	Propranolol (and some other β-adrenoceptor blockers) Noradrenaline General anaesthesia Histamine H_2-receptor blockers Glyceryl trinitrate Indomethacin
Pathological		Congestive cardiac failure Hepatic cirrhosis Circulatory collapse Renovascular hypertension

be unaltered during halothane anaesthesia in the spontaneously breathing patient. Recent studies in volunteers, and in patients receiving halothane anaesthesia, have confirmed this by failing to demonstrate any significant decrease in propofol clearance in the latter group (Cockshott, 1985).

Under eucapnic conditions, increasing concentrations of nitrous oxide in oxygen result in decreases in hepatic artery, portal venous and total hepatic blood flow (Thomson et al., 1982). Studies in man, comparing the kinetics of etomidate by infusion to supplement nitrous oxide in oxygen or oxygen-enriched air, showed a higher steady state drug concentration in the former group, accompanied by a greater AUC (Sear et al., 1984). Although a definite relationship has been found between MAC multiples of the inhalation agents and the associated blood concentrations, this has not been found to be as rigorously true for those i.v. agents studied to date. In general, these changes in plasma drug concentration resulting from IPPV, hypo- or hyper-capnia, or the use of nitrous oxide, do not appear to cause significant dynamic effects.

Pathological factors

When cardiac output is pathologically decreased, as in congestive cardiac failure, the splanchnic circulation becomes vasoconstricted, with a decrease in clearance of high ER drugs, and drug toxity (for example, lignocaine) (Thompson et al., 1973). In circulatory shock, Benowitz and colleagues (1974) found the decrease in lignocaine clearance to be greater than would be expected from the simple perfusion limited model—suggesting that hepatic ischaemia may cause a simultaneous further decrease in intrinsic clearance.

Hepatic disease. In liver disease, there are associated defects of hepatic blood flow (with intra- and extra-hepatic shunting) and of hepatocellular function (table IX). Boobis and colleagues (1980) have shown significant decreases in cytochrome P450 and aryl hydrocarbon hydroxylase activity in patients with cirrhotic liver disease, although Ahmed and Black (1977) found no such reduction in patients with cholestatic liver disease. In addition, there is often a decreased plasma protein binding in patients with cirrhosis or hepatitis, leading to an increased free drug fraction, with accompanying changes in the distribution and elimination of drugs. The effect of liver disease on the binding of i.v. agents is shown in table X. Because of these alterations in binding, there may be an increase in pharmacological activity following a single dose of a drug, and hence the risk of toxic side effects occurring during the induction of anaesthesia. However, there are no studies available to date looking at the influence of liver disease on the dynamics (intensity and duration) of the i.v. hypnotic agents. The overall influence of liver disease on the disposition of those drugs used for the induction or maintenance of anaesthesia is shown in table X. For further information, the reader should refer to a review by Williams and Benet (1980).

Renal disease. The major kinetic changes in patients with chronic renal disease are related to alterations in plasma protein binding and volumes of drug distribution, altered cellular metabolism and altered drug elimination.

In uraemia, the *plasma protein binding* of basic drugs is unaltered, but there is a significant decrease in the binding of acidic drugs that bind mainly to albumin. As a result an increased volume of drug distribution and increase in total drug clearance may be found. However, free drug clearance will be unaltered (Sear, Bower and Potter, 1986). There are three possible mechanisms for the decrease in protein binding: (i) uraemia itself: the high circulating urea

TABLE IX. *Predominant pathophysiological changes in various types of liver disease.* (*Adapted from Blaschke* (*1977*) *with permission of the author and publishers of* Clinical Pharmacokinetics)

Disease	Total liver blood flow	Hepatocellular mass	Hepatocellular function
Cirrhosis			
Mild	↓	↔ or ↑	↔
Severe	↓ ↓	↓	↓
Acute inflammatory liver disease			
Viral hepatitis	↔ or ↑	↔ or ↓	↓
Alcoholic hepatitis	↔ or ↓	↑, ↔ or ↓	↓

TABLE X. *Effect of liver disease (cirrhosis) on the kinetics of i.v. induction agents (expressed as % change from control healthy patients reported in the same study).* $T_{\frac{1}{2}}^{\beta}$ *= elimination half-life;* V_D *= volume of distribution;* Cl_P *= clearance;* Cl_{int} *= intrinsic hepatic clearance; Free fraction = unbound drug.* $^*P < 0.05$

	$T_{\frac{1}{2}}^{\beta}$	V_D	Cl_P	Cl_{int}	Free fraction
Thiopentone					
Pandele et al. (1983)	+35	+52	+13	−36	+74*
Ghoneim and Pandya (1975)					+89*
Methohexitone					
Richter et al. (1980)			+17		
Hexobarbitone					
Zilly, Breimer and Richter (1978)	+50*	−8	−43*		
Etomidate					
Bonnardot et al. (1982)	+79	−22	−56		
Althesin					
Sear (1981)	+31	+222*	−44		
Diazepam					
Klotz, Avant and Hoyumpa (1975)	+126*	+54*	−44*		+144*
Midazolam					
MacGilchrist et al. (1986)	+144*	+32	−48*		

concentration may affect the protein structure and its tertiary configuration, so altering the ability of the drug receptors to bind the drug molecules.

(ii) hypoalbuminaemia: this is the result of both increased excretion (as in the nephrotic syndrome) and decreased synthesis.

(iii) competition for drug binding sites: endogenous substrates and metabolites accumulate in renal failure, and may preferentially bind to plasma proteins.

Ghoneim and Pandya (1975), Burch and Stanski (1982) and Christensen, Andreasen and Jansen (1983) have all reported a decrease in the binding of thiopentone in renal failure. As a result, significant changes occur in drug clearance and distribution (table XI). However, in general, there are no changes in free drug or intrinsic clearance, or in the free drug volume of distribution in renal failure. The increase in free drug fraction may be the explanation for the reduced dose requirements for thiopentone in patients with renal failure (Dundee and Richards, 1954). However, while the increased free fraction may lead to higher brain and heart concentrations following a rapid i.v. bolus of thiopentone, this effect will be only transient. Burch and Stanski (1982) have suggested that, in the absence of any alteration in brain or CNS sensitivity to thiopentone in the uraemic patient, the pronounced cardiovascular and central nervous system depression of the normal induction dose will be prevented by a decrease in the rate of drug administration. The dose required for induction of anaesthesia will remain unaltered because the underlying free drug volume of distribution and free drug clearance are unchanged. This hypothesis has been supported by the studies of Christensen and Andreasen (1978) and Christensen, Andreasen and Jansen (1983), who compared the dose of thiopentone (in mg kg^{-1}) required to induce anaesthesia in patients with renal failure and in healthy patients. No differences were found, and the arterial and venous sleep concentrations of thiopentone were similar in both groups—indicating no change in CNS thiopentone sensitivity.

Uraemia has little effect on the major pathways of *hepatic drug metabolism* (oxidation and glucuronidation), although it may reduce the efficacy of hydrolytic and reductive metabolism. Reidenberg, James and Dring (1972) showed renal failure to cause significant prolongation of the elimination half-life of procaine. In addition, there is some evidence of an increased bioavailability of orally administered drugs in renal failure (Bianchetti et al., 1976).

Apart from reports on the plasma protein binding of etomidate (Carlos, Calvo and Erill, 1979) and preliminary data on the kinetics of propofol (Morcos and Payne, 1985), thiopentone is the only hypnotic agent to have been thoroughly investigated from a dynamic and kinetic standpoint in patients with renal failure. Studies with

TABLE XI. *Effect of renal disease (chronic renal failure) on the kinetics of i.v. induction agents, and benzodiazepines (expressed as % change from control healthy patients reported in the same study.* $T^{\beta}_{\frac{1}{2}}$ = *elimination half-life;* V_D = *volume of distribution;* Cl_P = *clearance;* Cl_{int} = *intrinsic hepatic clearance; Free fraction = unbound drug.* *$P < 0.05$

	$T^{\beta}_{\frac{1}{2}}$	V_D	Cl_P	Cl_{int}	Free fraction
Thiopentone					
Burch and Stanski (1982)	−4	+58*	+41*	−18	+78*
Christensen, Andreasen and Jansen (1983)	+82	+98*	+26	−34*	+77*
Ghoneim and Pandya (1975)					+97*
Etomidate					
Carlos, Calvo and Erill (1979)					+74*
Propofol					
Morcos and Payne (1985)	+79		+11		
Diazepam					
Ochs et al. (1981)	+152*	+33	+176*	−22	+384*
Midazolam					
Vinik et al. (1983)	−7	+74*	+69*	+7	+66*
Lorazepam					
Verbeeck, Tjandramaga and Verberckmoes (1976)	−15				
Alfentanil					
Sear, Bower and Potter (1986)	−22	+67	+94*	+50	+15*

the benzodiazepines show altered disposition of diazepam and midazolam, but not of lorazepam, in renal failure (table XI).

Pharmacological factors

Several drugs given intercurrently to patients undergoing general anaesthesia may affect the distribution and clearance of i.v. agents. These include the beta-adrenoceptor antagonists, H_2-receptor antagonists, calcium channel blockers, prostaglandin synthase inhibitors and the anti-arrhythmic agent, amiodarone.

Beta-adrenoceptor antagonists decrease total liver blood flow, and so reduce the clearance of flow-limited drugs (Branch et al., 1973; Sear and Prys-Roberts, 1982). In addition, Greenblatt, Franke and Huffman (1978) have shown propranolol to impair clearance of antipyrine—a drug of the capacity-limited, low ER group.

H_2-Histamine receptor antagonists (cimetidine and ranitidine) decrease the clearance of a number of drugs, for example chlormethiazole (Shaw et al., 1981) and fentanyl, in the dog although not in man (Lauwen et al., 1981; Borel et al., 1982). More recently, Klotz, Arvela and Rosenkranz (1985) have demonstrated an effect of a single dose of cimetidine 800 mg, but not ranitidine 300 mg, on the steady state midazolam concentration during constant rate infusion. A similar increase has been reported in the steady state concentration of diazepam in the presence of cimetidine (Klotz and Reimann, 1981). The action of cimetidine appears to be through binding to cytochrome P450 (Pelkonen and Puurunen, 1980). As a result, there is a decrease in phase I microsomal metabolism, but no apparent effect on phase II drug glucuronidation.

Some of the calcium channel blocking drugs (verapamil and nifedipine) act to increase total liver blood flow by vasodilatation (Feely, 1984; Bauer et al., 1986). This effect is not seen with diltiazem. By comparison, both verapamil and diltiazem reduce the clearance of antipyrine—indicating an impairment of microsomal drug metabolism (Bauer et al., 1986; Carrum et al., 1986; Egan, Abernethy and Mitchell, 1986). Whether chronic ingestion of these drugs will lead to significant changes in i.v. agent drug disposition, with accompanying altered dynamic responses, is uncertain at present.

In a single cross-over volunteer study, Feely and Wood (1982) have reported a decreased clearance and increased half-life of ICG, following chronic ingestion of indomethacin, a prostaglandin synthase inhibitor.

In a recent paper, Barry and colleagues (1986) have demonstrated inhibition of hepatic oxidative drug metabolism in the rat by amiodarone. They observed both a decrease in cytochrome P450 and a prolongation of the aminopyrine breath test half-life. Interestingly, chronic ingestion was not associated with a longer half-life—despite a significantly lower cytochrome P450 activity. This effect of amiodarone may be highly relevant to perioperative drug metabolism in man, as the elimination half-life of the drug is of the order of 100 days.

Overall, the significance of these drug–drug interactions lies in the possible alteration of the efficacy of agents with narrow therapeutic concentration ranges, or low therapeutic indices.

Influence of age on plasma concentrations of i.v. drugs

The kinetic profile of most i.v. drugs is altered in the elderly, as a result of a decline in both renal and hepatic clearance. In addition, the elderly show changes in body composition and drug–protein binding (Greenblatt, Sellers and Shader, 1982).

Renal clearance. The glomerular filtration rate (GFR) decreases in old age, with a mean decrease of 35% compared with young adults. Thus, the clearance of drugs excreted unchanged via the kidney (for example digoxin, cimetidine, chlorpropamide) will decline in parallel with the decrease in GFR.

Hepatic clearance. Cardiac output declines by 1% per year beyond the age of 20 yr, resulting in an estimated 40–45% reduction in hepatic blood flow in the elderly. There is also a decrease in hepatic cell mass.

The degradation of drugs in the liver may be affected by ageing. Hydroxylation and N-dealkylation activity are reduced in the elderly—so resulting in reduced clearance of bolus doses, and higher steady state drug concentrations during multiple dosage or infusion. There is a smaller effect of ageing on phase II glucuronide conjugation. Anomalies may occur, however. Thus decreased clearance in old age has been demonstrated for propranolol, but not for lignocaine; both are drugs with a high hepatic extraction ratio and, therefore, flow-dependent clearance.

There are few studies on the effect of ageing on the disposition of i.v. hypnotic agents. In a comparison of thiopentone kinetics in young and elderly women, Christensen, Andreasen and Jansen (1981) showed the elderly to have greater volumes of distribution, longer half-lives and higher serum clearance, presumably as a result of changes in drug binding. The kinetics of diazepan, however, show a decreased clearance in the elderly (Greenblatt et al., 1980; Macklon et al., 1980). Preliminary data for elderly patients receiving propofol for induction of anaesthesia suggest a decreased clearance (I. Cockshott, personal communication), and this would support the clinical observations of Hilton, Dev and Major (1985) that the elderly require lower infusion rates to maintain anaesthesia.

Induction doses of alfentanil 50 $\mu g\ kg^{-1}$ have altered kinetics in the elderly (Helmers et al., 1984), together with prolonged dynamic effects—that is, the duration of adequacy of anaesthesia (Helmers, Noorduin and Leeuwen, 1985). However, there appears to be no alteration in brain sensitivity to alfentanil in the elderly, when measured as the blood concentration at which anaesthesia needed to be supplemented by a volatile agent. Similar prolongation of the half-life of opiates in the elderly has been described for fentanyl (Bentley et al., 1982). For potent opiate drugs, altered kinetics may result in prolonged clinical effects, for example sedation and respiratory depression at the completion of surgery.

In addition to changes in drug disposition in old age, there is evidence for enhanced sensitivity of the elderly to nitrazepam and warfarin (Castleden et al., 1977; Shepherd et al., 1977). Roizen and colleagues (1985) have shown ageing to exaggerate the haemodynamic responses to induction of anaesthesia and surgical incision in patients receiving thiopentone–fentanyl and isoflurane anaesthesia.

Drug Interactions

These may be classified into two main groups: those beneficial to the patient, and those which are not. From a pharmacological viewpoint, interactions may be either pharmaceutical, pharmacokinetic or pharmacodynamic in origin.

Pharmaceutical interactions

Physicochemical incompatibility is not uncommon, and may be manifest as the formation of a precipitate or cloudiness following the mixing of drug solutions. However, absence of a precipitate does not exclude the possibility of a significant reaction occurring.

Aqueous solubility and pH. Most i.v. drugs are highly lipophilic and will, therefore, have a low aqueous solubility. As a result, use of a solubilizing agent may be necessary (for example with etomidate, propofol and diazepam). Excess dilution of these drugs may lead to the solution becoming unstable. A second feature of lipophilic drugs may be pH dependent solubility which depends upon the extent of ionic dissociation. Thus acidic drugs (e.g. thiopentone and methohexitone) are most soluble at high pH (pH 10–11), while basic drugs (e.g. ketamine) are formulated at a low pH (pH 3.5–4.0). Changes in pH may lead to precipitation of the drug from solution.

I.v. solutions. The addition of drugs to blood, blood products, plasma expanders, fat emulsions or solutions containing mannitol, sodium bicarbonate or amino acids may result in altered bioavailability, through either incompatibility and precipitation, or changes in binding. Straathof and colleagues (1984) have described a significant effect of infusions of Intralipid on the disposition of phenytoin in the rat, while the increased induction dose of the emulsion formulation of propofol, compared with that determined using the Cremophor EL formulation, may reflect an increased drug binding to liposomes (Cummings et al., 1984).

Neuromuscular blocking drugs. Both thiopentone and methohexitone interact with suxamethonium to cause rapid hydrolysis of the relaxant because of their high pH, and barbituric acid is precipitated. Tubocurarine, alcuronium, pancuronium and atracurium also form precipitates when administered through the same i.v. infusion as thiopentone.

Pharmacokinetic and pharmacodynamic interactions

Pharmacokinetic interactions may alter the distribution, binding, metabolism or elimination of a drug. Examples related to the i.v. agents are the influence of solubilizing agent on the kinetics of diazepam (Fee et al., 1984) and the prolongation of the action of suxamethonium by propanidid. (Monks and Norman, 1972).

Barbiturates and other hypnotic drugs have been reported to show a prolonged action in both man and animals receiving monoamine oxidase inhibitors, and tricyclic antidepressants. This is presumably a result of the latter inhibiting liver microsomal oxidase activity. A similar inhibitory effect may be the cause of the decrease in etomidate clearance in the presence of fentanyl (Schüttler et al., 1983).

MINOR SEQUELAE ASSOCIATED WITH I.V. AGENTS

Although Dundee (1979) has defined the characteristics of the ideal i.v. induction agent, none to date has fulfilled all of the criteria. The minor adverse features of drugs used for the induction and maintenance of anaesthesia may be considered as: induction complications, recovery, duration of action and cumulation, and tissue irritation and damage.

Induction complications

Excitatory phenomena (involuntary movements, hypertonus) are seen with all i.v. agents when given to the unpremedicated patient. However, the incidence varies between agents, thiopentone having an incidence of about 8%, while muscle movements following etomidate may be as high as 95% (Dundee, 1963; Zacharias, Dundee and Clarke, 1978). Comparable figures for other i.v. agents are 30–35% for methohexitone, and 14% for propofol (Dundee, 1963; Stark et al., 1985). For all drugs, the incidence seems to depend principally on the dose of drug administered, and the use or not of premedication.

Neurolept drugs used to induce anaesthesia may cause muscle rigidity and laryngospasm. These can be abolished by the simultaneous administration of neuromuscular blocking agents.

Respiratory upsets (cough, hiccup and laryngospasm) are seen in significant frequency (40–45%) only with methohexitone (Young and Whitwam, 1964). With the benzodiazepines and other hypnotic agents the incidence is extremely low.

The barbiturates may, however, cause respiratory depression in up to 70% of patients (Whitwam, 1962). Fry, Whitwam and Chakrabarti (1973) have suggested that the extent of this depression is increased by pre-oxygenation—as a result of the reduction in peripheral chemoreceptor activity. Hyperventilation may occur after induction with etomidate and methohexitone and may be followed by apnoea in 30% of patients receiving etomidate (Morgan, Lumley and Whitwam, 1977). Apnoea is also seen following induction of anaesthesia, and maintenance by infusion, using propofol. The respiratory depressent effects of diazepam and midazolam are minimal, but may be enhanced by opiate premedication.

Recovery

Patients in the recovery room are often restless, and show emotional lability. However, the use of ketamine for induction of anaesthesia may be followed by hallucinations, delirium and visual disturbances. These symptoms can be partially eliminated by avoiding patient stimulation during recovery, and by use of benzodiazepines as premedication.

Increased muscle tone may occur during recovery, just as is seen during induction. Anaesthesia induced with etomidate and ketamine are often followed by these sequelae.

There is much interest in the development of i.v. agents which allow induction of anaesthesia and also possess analgesic properties. Only ketamine has such properties, while Clutton-Brock (1961) showed the barbiturates to depress pain threshold—that is, they are "anti-analgesic". Benzodiazepines appear to have no effect on the pain threshold.

Tissue irritation

All of the i.v. hypnotic agents used for the induction of anaesthesia can cause pain on injection, and postoperative venous sequelae. The incidence of pain on injection differs between studies for individual agents; thus various studies reported by Dundee (1979) showed a range between 10 and 63% for etomidate. By comparison, the incidence for thiopentone has been recently reported in 123 patients to be zero when the drug is given into veins of the forearm or antecubital fossa and 7.5% when injected to the dorsum of the hand (Stark et al., 1985). In this same review, the comparable incidences for methohexitone and propofol were 6.8% and 6.0%, respectively, when given into the veins of the antecubital fossa and 40.5% and 28.5% for the dorsum of the hand.

Schou-Olesen, Hüttel and Hole (1984) compared the incidence of pain on injection and postoperative venous sequelae in a double-blind study of 65 patients receiving either thiopentone 5 mg kg^{-1} or etomidate 0.3 mg kg^{-1}. Twenty-four per cent of patients noted pain with etomidate; none with thiopentone. The incidence of thrombophlebitis was greater (24%) in the etomidate group compared with thiopentone (4%). Interestingly, the incidence of thrombophlebitis was lower than the 48% seen following administration of diazepam in the same solvent, propylene glycol (Schou-Olesen and Hüttel, 1980).

TABLE XII. *Incidence of venous thrombosis at 2nd or 3rd day after anaesthesia in female patients undergoing minor gynaecological or body surface surgery. †Assessed at 24 h. PEG = polyethylene glycol: PG = propylene glycol. (Adapted from Dundee (1979) with permission of the author and publishers of* Intravenous Anaesthetic Agents*; and Stark et al. (1985))*

	Formulation	Incidence (%)
Thiopentone	2.5%	2.0
	5.0%	5.8
Methohexitone	1.0%	3.0
	2.0%	6.3
Althesin	In Cremophor	3.0
Etomidate	Aqueous	10.8
	PEG	7.7
	PG	23.4
Propofol	Emulsion	0.5†

Table XII summarizes the incidence of postoperative venous sequelae for etomidate (administered as three different formulations), thiopentone, methohexitone, propofol and Althesin.

Use of diazemuls, an emulsion formulation of diazepam, is associated with a low incidence of thrombophlebitis, and only a 4% incidence of pain to injection (von Dardel et al., 1983). Midazolam, a water soluble benzodiazepine, has also been reported to cause a low incidence of venous complications (Jensen, Hüttel and Schou-Olesen, 1981).

In a comparison of i.v. diazepam, lorazepam and flunitrazepam, Hegarty and Dundee (1977) reported an overall 39% incidence of venous sequelae with diazepam, and significantly lower rates for the other two agents: 15% and 5%, respectively.

The accidental injection of i.v. agents directly to an artery may result in marked sequelae (MacIntosh and Heyworth, 1943). Thiopentone and methohexitone both precipitate out of solution when injected to an artery, as a result of the decrease in pH. In addition, red cell haemolysis and platelet aggregation occur, leading to intravascular thrombosis. Severe tissue necrosis resulting in amputation of the affected tissue has been reported in three patients, to whom diazepam was accidentally injected i.a.

CONCLUSIONS

Despite the development of newer i.v. agents, adverse and toxic side effects still occur. These effects may be caused by the agent itself or by the solvent in the case of those with low water solubility.

Two drugs, propofol and midazolam, seem to offer some advantages over thiopentone for induction of anaesthesia, but neither drug has yet been fully evaluated for use by continuous infusion for the maintenance of anaesthesia. Let us hope any adverse and toxic effects of these, and further i.v. agents, are determined before the drugs become established in clinical practice. The withdrawal of Althesin, and limitations over the use of etomidate, have left a niche for other non-cumulative agents in the development of i.v. infusion anaesthesia.

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ADVERSE EFFECTS OF NEUROMUSCULAR BLOCKING DRUGS

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Neuromuscular blocking drugs are not as notorious for producing adverse reactions as the i.v. induction agents; nevertheless, to a varying degree they all produce unfavourable or harmful effects. The newer non-depolarizing neuromuscular blockers, atracurium and vecuronium, have been developed in an attempt to overcome the disadvantages of the earlier drugs, but although much more specific agents, they are not completely free from side-effects. The adverse effects of the neuromuscular blocking drugs available in Great Britain today will be discussed in this paper. Those which are not available in this country (such as pipecuronium and metocurine), and obsolete agents (such as decamethonium) will not be discussed. Although what follows is concerned mainly with the non-depolarizing agents, suxamethonium is included where appropriate, whilst what might be regarded as the unique features of the drug are discussed later in the article.

DIRECT CARDIOVASCULAR EFFECTS

With the possible exception of vecuronium, all the neuromuscular blocking drugs have some effect on the cardiovascular system. Such effects are described usually in terms of the degree of ganglionic blockade, sympathetic stimulation, vagal stimulation and vagolytic effect, and are summarized in table I. It must be emphasized, however, that histamine release caused by administration of a blocking agent may well have a much greater effect on the cardiovascular system than any direct effect of the drug itself; this is particularly pertinent in the case of tubocurarine.

The ganglionic blockade caused by tubocurarine and the synthetic derivative of tubocurarine, alcuronium, results in a decrease in peripheral vascular resistance and hence a reduction in arterial pressure. This effect is dose related and is probably of clinical significance only when using larger doses of the drugs (such as tubocurarine 0.6 mg kg^{-1}) and in a hypovolaemic patient. As tubocurarine also releases histamine to a significant degree, the two unrelated effects may combine, even when using smaller doses of this drug to produce a decrease in arterial pressure, an effect which is often used to clinical advantage when hypotension is desired.

The sympathomimetic effect characteristic of some neuromuscular blocking drugs is thought to be an indirect response attributable to release of noradrenaline from adrenergic nerve endings in the heart; it has been demonstrated with both gallamine (Brown and Crout, 1970) and pancuronium (Nana, Cardan and Domokos, 1973). The

TABLE I. *The pharmacological effects of each of the neuromuscular blocking drugs which produce cardiovascular changes.* (*From Norman* (*1985*))

	Ganglion blockade	Sympathetic stimulation	Vagolytic effect	Vagal stimulation	Histamine release
Suxamethonium	−	−	−	+	+
Vecuronium	−	−	−	−	−
Atracurium	−	−	−	−	+
Alcuronium	+	−	−	−	+
Gallamine	+	+	+++	−	+
Tubocurarine	++	−	−	−	+++
Pancuronium	−	++	++	−	−

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subsequent development of tachycardia and hypertension is potentiated by the vagolytic effect of these two drugs, for they also produce an atropine-like blockade of the cardiac muscarinic receptors (Goat and Feldman, 1972).

In contrast, of all the neuromuscular blocking drugs, suxamethonium is most likely to produce a reduction in heart rate as a result of stimulation of the cholinergic receptors in the heart, either directly or indirectly from reflex activity following stimulation of peripheral sensory receptors in the carotid body. There has been much discussion in the literature over these alternative mechanisms and the relative importance of each is still not clear (Goat, 1972). Bradycardia and asystole have been described clinically after a single dose of suxamethonium (Sorenson et al., 1984), but this effect on muscarinic receptors is more pronounced after repeated dosage, in the presence of an inhalation agent and in the younger patient (Leigh et al., 1957). In such circumstances, the resultant bradycardia frequently necessitates the use of an anticholinergic drug such as atropine.

In a patient with severe cardiovascular disease the cardiovascular effects produced by a neuromuscular blocker can be of clinical importance: for instance gallamine might be contraindicated because the combination of a vagolytic effect with sympathetic stimulation may cause an unacceptable increase in heart rate and hence cardiac rate–pressure product (Stoelting, 1973). The same effect, to a lesser extent, may also be seen with pancuronium.

Atracurium and vecuronium are free from direct cardiovascular effects within the clinical dose range (Crul and Booji, 1980; Sokoll et al., 1983), although the histamine releasing properties of atracurium may produce some degree of hypotension and tachycardia, especially when used in large bolus doses, greater than 0.6 mg kg^{-1} (Hughes and Payne, 1983). Only when very large doses (2 mg kg^{-1}) were used in animal work has a vagolytic effect been reported with atracurium (Hughes and Chapple, 1980). Because of the possibility of histamine release with atracurium, vecuronium is the neuromuscular blocking agent causing the least cardiovascular side effects. It is therefore the best drug when considering the most suitable form of anaesthesia for the patient with severe myocardial disease.

The virtual absence of direct cardiovascular effects associated with vecuronium and atracurium, however, does allow other anaesthetic agents such as halothane and the opioid analgesics to exert an unopposed effect on the myocardium. In addition, surgical manoeuvres which result in vagal stimulation such as peritoneal traction or cervical stimulation may lead to an unopposed reduction in heart rate. These factors probably explain the occurrence of bradycardia which has been reported during the use of both atracurium (Carter, 1983) and vecuronium (Robertson, et al., 1983) which provoked much debate in the literature (Madden, 1983; Macrae, 1985). It is pertinent that a similar case of sinus arrest during peritoneal traction has also recently been reported when tubocurarine was the neuromuscular blocking agent used (Nandi and Astley, 1985); there is always the possibility of a bradycardia during vagal traction, whatever the anaesthetic technique used.

HISTAMINE RELEASING PROPERTIES

Most neuromuscular blocking agents cause histamine release and the results of this release are seen in three ways: first, by a local erythematous reaction, like nettle rashing, sometimes accompanied by a widespread flush but without a reduction in arterial pressure; second by systemic effects such as tachycardia and hypotension, which may well be of clinical importance; and third, and rarely, as a life threatening anaphylactic or anaphylactoid reaction.

Basic compounds are more disruptive of mast cells, and thus more prone to release histamine than are acidic substances. Of the neuromuscular blocking agents, tubocurarine is the most potent in this respect: the free hydroxyl groups on the molecule are thought to enhance histamine release. Atracurium (Hilgenberg, 1983), alcuronium and gallamine have only about one-third of the histamine releasing potency of tubocurarine. However, several severe anaphylactic reactions to all these agents have now been described (Salem, Kim and El Etr, 1968; Fisher, 1978; Fisher, Hallowes and Wilson, 1978; Mercer, 1984). Although pancuronium and vecuronium, which are acidic compounds, are relatively free from histamine releasing properties, cardiovascular collapse has been reported following the administration of pancuronium, as has an incident of acute bronchospasm following administration of the drug (Heath, 1973; Mishima and Yamamura, 1984). More recently, localized histamine release has been reported after an injection of vecuronium (Spence and Barnetson, 1985).

It has been suggested that atracurium does not cause histamine release when doses of less than 0.6 mg kg^{-1} are used. It has also been demonstrated that histamine liberation is less likely to become evident when the speed of administration of atracurium is reduced and when pretreatment with H_1 and H_2-receptor antagonists is used; cimetidine 4 mg kg^{-1} and chlorpheniramine 0.1 mg kg^{-1} i.v. were given successfully for this purpose (Scott et al., 1985). It is probable that the same histamine antagonists would have similar beneficial effects with the other histamine releasing neuromuscular blockers, especially tubocurarine.

The incidence of the localized erythema and urticaria occasionally produced when atracurium is injected to a peripheral vein may be reduced by injecting the drug separately from the induction agent, either by flushing the needle used with saline between the administration of two drugs or by injecting them both to a free flowing peripheral i.v. infusion. This observation suggests that the precipitate formed by the mixture of the two drugs is responsible at least in part for the localized response (Hughes, 1985).

There is some evidence that allergic cross reactivity between different myoneural blockers can develop, exposure to a second blocker more commonly producing any abnormal reaction when sensitivity to another relaxant has already occurred (Harle, Baldo and Fisher, 1985).

There are isolated reports of anaphylactoid reactions to suxamethonium (Assem, Frost and Levis, 1981; Royston and Wilkes, 1978), but these are generally considered to be much less common than with tubocurarine (Lim and Churchill-Davidson, 1981).

IMPAIRED METABOLISM AND EXCRETION

Any pathological process which impairs the route of metabolism or excretion of a neuromuscular blocking drug may result, not only in prolongation of the effect of the drug, but also in difficulty in antagonizing the residual neuromuscular blockade. Apart from the enzymatic or spontaneous breakdown of suxamethonium and atracurium that occurs in plasma and extracellular fluid, the liver and kidney are the two main organs involved in metabolism and excretion of neuromuscular blockers. (The metabolism of suxamethonium may be prolonged either by inherited abnormalities of pseudocholinesterase or by several acquired factors which will be discussed later.)

TABLE II. *The percentage of each neuromuscular blocker excreted in the urine (Miller, 1985)*

Neuromuscular blocker	Percent excreted
Gallamine	> 95
Alcuronium, pancuronium	60–90
Tubocurarine	25–60
Vecuronium	3.5
Suxamethonium, atracurium	None

TABLE III. *The percentage of each neuromuscular blocker recovered in the bile over 24 h after a bolus dose (Duvaldestin, Lebrault and Chauvin, 1985)*

Neuromuscular blocker	Percent recovered
Alcuronium	15–20
Tubocurarine	12
Pancuronium	10
Vecuronium	12
Gallamine	< 0.5

Non-depolarizing neuromuscular blockers are highly ionized, water soluble substances which are filtered by the renal glomerulus and, unlike lipid-soluble substances, are not reabsorbed in the proximal tubule. The kidney is, therefore, the main route of excretion of gallamine, tubocurarine, alcuronium and pancuronium (table II). In addition, some excretion of all these drugs (except for gallamine) occurs into the bile (table III) together with metabolic transformation to more water soluble, less pharmacologically active breakdown products in the liver, the resultant metabolites also being excreted both into the bile and through the kidney. In contrast, vecuronium is mainly metabolized in the liver by deacetylation, in a manner similar to the metabolism of pancuronium, but much more extensively. So extensively, indeed, that the proportion of free drug excreted in the urine is much smaller than in the case of other conventional non-depolarizing neuromuscular blocking agents (Upton et al., 1982).

Hepatic disease

The need for abnormally high doses of competitive blockers such as tubocurarine in cirrhotic liver disease to obtain a satisfactory effect (resistance) has long been recognized (Dundee and Gray, 1953). A similar phenomenon has been reported in cirrhotic patients, together with difficulty in antagonism of block following pancuronium (Duvaldestin et al., 1978) and following the use of large doses of vecuronium (0.2 mg kg^{-1}) (Hunter, Parker et al., 1985; Lebrault et al., 1985). Resistance to atracurium has also been encountered in a patient with a large liver abscess and abnormal liver function (Gyasi and Naguib, 1985).

In obstructive liver disease an increased volume of distribution of pancuronium has been shown with consequent prolongation of effect (Westra, Keulemans et al., 1981; Westra, Vermeer et al., 1981). In contrast gallamine, which is excreted entirely by the kidney, was found by the same workers to have a pharmacokinetic profile in obstructive liver disease similar to that of healthy subjects.

In clinical practice, the difference in the pharmacokinetics and pharmacodynamics of non-depolarizing neuromuscular blocking drugs in patients with cirrhotic as opposed to obstructive liver disease is probably unimportant. It seems probable that, in all these oedematous patients, an increased volume of distribution of the loading dose of the drug results in apparent initial resistance to the effects of the blocker. The impairment of liver function in these cases, however, results in a decreased rate of metabolism of any drug metabolized in that organ. Prolonged action of the blocker thus ensues as the elimination of the agent then depends mainly on the kidney, although redistribution, perhaps to non-specific receptors, will influence clinical antagonism. Such redistribution is usually sufficient to ensure clinical recovery after a single dose of blocker, but after repeated incremental doses difficulty in obtaining satisfactory antagonism of residual blockade frequently ensues.

In addition to the altered pharmacodynamics of non-depolarizing neuromuscular blocking agents in the presence of liver disease, a great variation between patients in the duration of action of equivalent doses of such drugs is recognized. For many years attempts have been made to relate altered plasma protein concentrations, and the degree of plasma protein binding, to this marked variation. Unfortunately, different methods of assay appear to give widely different results and it now seems that there is little difference in the percentage of plasma protein binding of either tubocurarine, pancuronium or vecuronium in cirrhotic patients compared with healthy controls (Meijer et al., 1979; Duvaldestin and Henzel, 1982).

Renal disease

With the exception of suxamethonium and atracurium, which are broken down in plasma, all neuromuscular blocking drugs are excreted at least in part by the kidney (table II).

Before the advent of atracurium and vecuronium, tubocurarine was widely considered to be the drug of choice in patients with renal failure, albeit in reduced dosage, because this was the only agent for which biliary excretion had been shown to be increased in the absence of renal function (Cohen, Brewer and Smith, 1967). The obvious problem with all the neuromuscular blockers which are largely excreted by the kidney is that prolonged curarization may be seen after their use, and this is particularly so after repeated incremental doses (Gibaldi, Levy and Hayton, 1972). This manifests itself as a poor antagonism of residual neuromuscular blockade in the presence of a residual amount of the relevant blocker in the plasma, with resultant respiratory embarrassment and acidosis.

There is a wide range in the degree of residual blockade that may remain: in some patients it may be minimal, being manifest only as diplopia (Hunter, Jones and Utting, 1984) or it may be extreme and require artificial ventilation for several hours, or even days (Riordan and Gilbertson, 1971). As gallamine is almost totally excreted by the kidney, it is not surprising that there are reports in the literature of renal failure patients receiving artificial ventilation for several days after a single dose of the drug (Churchill-Davidson, Way and de Jong, 1967). It is contraindicated in the anephric patient.

Atracurium and laudanosine. There are now several reports of the successful use of atracurium in anephric patients (Hunter, Jones and Utting, 1982b; Fahey et al., 1984). Concern has been expressed, however, that the major break-down product, laudanosine, which in large doses is known to produce epileptiform seizures in dogs (Chapple, Miller and Wheatley, 1985) may have similar adverse effects in humans, especially in renal failure patients, since it is excreted mainly by the kidney (Fahey et al., 1985). The concentrations of laudanosine detected by these workers in renal transplant patients were, however, much smaller than those necessary to induce seizures in experimental animals. Prolonged infusions of atracurium to patients in renal failure, for example, in the intensive therapy unit might result in high blood concentrations of laudanosine, however. A recent report suggests that such infusions can be used safely, even in patients with renal failure, for up to 36 h (Griffiths, Hunter and Jones, 1986). Nevertheless, further study is needed to establish the safety of long-term infusions of atracurium in such patients, particularly with regard to serum laudanosine concentrations.

As a result of animal studies it has also been suggested that, in the presence of plasma concentrations of laudanosine comparable to those found in humans after the administration of a bolus dose of atracurium, the MAC value for halothane is increased (Shi et al., 1985). These workers suggest that laudanosine may increase cerebral irritability and be responsible for an increase in anaesthetic requirement. There are at present, however, no clinical reports of experience in humans to support this hypothesis.

Vecuronium, which is only excreted unchanged to a small extent in the urine (Upton et al., 1982), also offers a significant advance in the treatment of patients with renal failure (Fahey et al., 1981; Hunter, Jones and Utting, 1984). There has, however, been a report of two cases of resistance to the drug in renal failure patients, both of whom were very sick; this phenomenon has not been satisfactorily explained (Hunter, Jones and Utting, 1984). Atracurium is probably the best drug for use in patients in renal failure.

Age

The duration of action of non-depolarizing neuromuscular blocking agents varies with the age of the patient. Neonates have been shown to be sensitive to tubocurarine (Bush and Stead, 1962), alcuronium (Bush, 1965) and pancuronium (Bennett et al., 1975) and, to a lesser extent, to atracurium and vecuronium (Brandom et al., 1983; Nightingale and Bush, 1983). Compared with adults, children of school age appear to be resistant rather than sensitive to non-depolarizing neuromuscular blocking drugs, and then with advanced age an increasing sensitivity develops. In the elderly this increased sensitivity is probably accounted for by slower metabolism and excretion of drugs, in contrast to the neonate, in whom it is more likely to be related to a decreased number of post-synaptic receptors. Thus a decreased clearance of pancuronium (McLeod, Hull and Watson, 1979), alcuronium (Stephens et al., 1984) and tubocurarine (Matteo et al., 1985) have all been demonstrated in the elderly. Both the onset and the duration of action of vecuronium 0.07 mg kg^{-1} have been shown to be prolonged in old age (d'Hollander et al., 1982; d'Hollander, Nevelsteen et al., 1983). D'Hollander's group did not find such prolongation with atracurium (d'Hollander, Luyckx et al., 1983), for which the responses were compatible with those reported clinically in the elderly for atracurium by Rowlands (1983). A recent pharmacokinetic study of single dose–response curves for vecuronium, using smaller doses of the drug (up to 0.04 mg kg^{-1}) has, however, suggested that there is no significant difference between the younger and older patient within this lower dose range (O'Hara, Fragen and Shanks, 1985). It would seem that the sensitivity to vecuronium in old age is probably partly related to dosage. It is possible, therefore, that atracurium is the drug of choice in elderly patients, but it is imperative that, with any neuromuscular blocker, care is exercised, particularly in respect to the need for a reduced dose in this age group.

NEUROMUSCULAR DISORDERS

Neuromuscular blocking agents act primarily at the post-synaptic membrane of the neuromuscular junction. It is therefore to be expected that patients who have a pathological process at this site, such as myasthenia gravis or those with muscle disorders, frequently show an abnormal response to neuromuscular blocking drugs. The primary problem in patients with these diseases is that the response to both depolarizing and non-depolarizing blockers is unpredictable. In addition, worse problems may occur when the disease is undiagnosed in the patient being anaesthetized. The subject has been fully reviewed by Azar (1984).

Myasthenia gravis

In this disease, which occurs more commonly in females, patients frequently present with weakness of cranial muscles, especially the ocular and oro-pharyngeal groups. Typically, this muscle weakness gradually spreads throughout the body, involving not only the limbs, but also the muscles of respiration. The degree of weakness varies from day to day, but is associated with excessive fatiguability of the muscle groups involved. No neurological deficit is demonstrable and patients show consistent improvement after therapy with cholinergic drugs. There is great variability in the rate of progression of the disease, and if resistance to cholinergic agents develops, steroids or other immunosuppressant drugs such as azathioprine are often introduced. Myasthenia gravis is frequently associated with hyperplasia of the thymus and, if tolerance also develops to immunosuppressant agents, thymectomy may be performed.

In pathological terms, myasthenia gravis is an autoimmune disease affecting the neuromuscular junction, in which the patients develop antibodies to the post-synaptic acetylcholine receptors, leading to a decrease in both their number and half-life. As the disease progresses, presynaptic receptors sites may also become affected and fade of the train-of-four twitch response may then be seen even before any blocking agent is given. The response of such patients to both depolarizing and non-depolarizing neuromuscular blocking drugs is unpredictable, depending to a certain extent on the degree and duration of the disease process. Churchill Davidson and Richardson (1953) were the first to report that myasthenia patients showed initial resistance to depolarizing neuromuscular blockers, followed by a dual block; this was later substantiated by Foldes and McNall (1962). In contrast, marked sensitivity was demonstrated to non-depolarizing blocking agents; for example, it was found that tubocurarine, in doses as small as 2 mg, produced a clinical block (Foldes and McNall, 1962).

It seems, however, that when myasthenic patients are in remission they may tolerate normal doses of non-depolarizing blockers; certainly this has been demonstrated in the case of pancuronium (Blitt, Wright and Peat, 1975). This may explain the normal response of some myasthenic patients to suxamethonium. Because of this variability in response, continuous neuromuscular monitoring is necessary when a neuromuscular blocking drug is required in the myasthenic patient.

Small doses of both atracurium (Baraka and Dajani, 1984; Bell et al., 1984) and vecuronium (Hunter, Bell et al., 1985) have been used safely in myasthenic patients and these agents appear to offer a substantial advantage over tubocurarine. The new blocking drugs may become the preferred agents in patients with myasthenia gravis in whom a neuromuscular blocker is required; certainly there is no longer an indication for deep inhalation anaesthesia in these patients.

There is a wide variation amongst clinicians in regard to the question of continuation or otherwise of anticholinesterase therapy immediately before surgery in the myasthenic patient. If therapy is stopped before operation then the patient is often very weak on presentation for surgery and, therefore, is less likely to need a blocking drug, or will need less of it. By the end of surgery, however, the patient is even weaker, and then larger doses of anticholinesterase may be indicated. It is probably preferable, therefore, to continue routine therapy until induction of anaesthesia.

Myasthenic syndrome

The appearance of proximal muscle weakness, having many of the features of myasthenia gravis, in patients with advanced carcinoma was first described by Henson, Russell and Wilkinson (1954) and the particular association of oat-cell carcinoma of the bronchus (in up to 1% of patients) with a similar myopathy was then noted by Eaton and Lambert (1957). In this syndrome, unlike myasthenia gravis, the patients are very sensitive to suxamethonium, in addition to the non-depolarizing neuromuscular blocking drugs, and they respond poorly to treatment with anticholinesterase. Also in contrast to myasthenia gravis, a growth in electromyograph potential on low frequency tetanic stimulation is seen, together with marked post-tetanic facilitation (Wise, 1962). This pattern probably explains the transient increase in muscle strength which may be seen on exertion in this condition, although this may be followed by a prolonged period of excessive fatigue. A typical anaesthetic presentation of such a case consists of a male patient undergoing bronchoscopy for possible carcinoma of the bronchus with failure to resume effective respiratory muscle action in the normal way following a single dose of suxamethonium.

Myotonic dystrophy

This is the commonest muscle dystrophy of adult life which also varies greatly in severity between patients, the mild form being associated with few symptoms or signs. It presents typically with facial weakness, producing an expressionless facies, ptosis, dysarthria, wasting and weakness of the sternomastoids and initially of the proximal muscle groups, followed later by progressive distal muscle involvement. Classically, the myotonia produces an inability to relax the grip. Myotonia dystrophia is a multisystem disease: other features include premature frontal balding and cataracts, testicular atrophy, low intelligence and myocardial conduction defects.

The use of neuromuscular blocking drugs in this inherited condition (autosomal dominant) has been recently reviewed by Aldridge (1985). Suxamethonium should be avoided as it may accentuate the myotonia, causing respiratory muscle spasm and subsequently airway problems, because the rigidity may make endotracheal intubation impossible. It has been suggested that the increase in serum potassium concentration produced by suxamethonium may be responsible for this increased rigidity, as marked hyperkalaemia has been shown experimentally to produce spontaneous myotonic discharges. As neostigmine has been reported to worsen the myotonia in myotonic dystrophy, it is probably more appropriate to allow spontaneous recovery after the use of a non-depolarizing neuromuscular blocker (Buzello, Krieg and Schlickewei, 1982). It has, therefore, been suggested that atracurium or vecuronium, which have shorter half-lives than the conventional myoneural blockers, are very useful agents in this condition (Nightingale, Healy and McGuinness, 1985). Finally, it must be remembered that these patients have a reduced muscle mass and therefore smaller doses of all blocking drugs are still indicated if excessive blockade is to be avoided.

Duchenne muscular dystrophy

This is another inherited condition, resulting from a sex-linked recessive gene and, therefore, seen mainly in males. It presents early in life, usually between 2 and 6 years, initially with a clumsy gait which gradually progresses to a complete inability to walk and confinement to a wheel-chair by 8–11 years. In addition to the progressive musculo-skeletal deformity, which spreads to the shoulder girdle muscles and causes fatty replacement of muscle tissue, obstructive cardiomyopathy frequently develops, evidence for which is detectable on the electrocardiogram and is accompanied by evidence of cardiac enlargement on the chest x-ray. The resting plasma creatinine phosphokinase concentration is frequently increased.

Affected patients often require orthopaedic surgical procedures (e.g. for the associated kyphoscoliosis) or surgery for incidental operations such as dental extraction. Following administration of suxamethonium or halothane they may develop a hyperpyrexic response similar to that characteristic of malignant hyperthermia, associated with a further increase in serum creatinine phosphokinase concentration, myoglobinuria and a metabolic acidosis which may lead to cardiac arrest. Not only may this occur during anaesthesia, but delayed respiratory insufficiency may occur several hours after a full recovery from an anaesthetic (Smith and Bush, 1985).

Malignant hyperthermia

It is now well accepted that suxamethonium should be avoided in this condition (Gronert, 1980). For many years pancuronium was considered to be the drug of choice in susceptible patients (Cain and Ellis, 1977), although, as neostigmine may precipitate a cholinergic crisis, it is considered preferable to allow spontaneous recovery from any non-depolarizing neuromuscular blocking agent (Ellis, 1980). In the case of the older non-depolarizing agents, this practice may prolong anaesthesia inconveniently and atracurium and vecuronium possess advantages in this respect. Satisfactory use of both agents has been reported in patients susceptible to malignant hyperpyrexia (Buzello et al., 1985; Michel and Fronefield, 1985), although prolongation of the duration of action of vecuronium has been observed in a susceptible patient pretreated with dantrolene (Driessen, Wuis and Gielen, 1985). Dantrolene, which mainly acts by interfering with calcium uptake into or release from the sarcoplasmic reticulum, has been shown, when given alone, to produce a dose-dependent depression of the mechanical twitch response and a prolonged decrease in grip strength (Flewellen et al., 1983). It is possible that similar problems may be encountered when other neuromuscular blocking agents are administered in the presence of this drug.

MISCELLANEOUS EFFECTS

Burns

A variety of causes were initially postulated for the cardiac arrests that were recognized to occur, albeit rarely, when the severely burned patient was anaesthetized; these included vagal stimulation, acidosis, fluid depletion, reduced concentrations of pseudocholinesterase, and overdosage of anaesthetic agents. Gradually it became apparent that hyperkalaemia induced by suxamethonium was the usual cause; in burned patients suxamethonium causes a more marked increase in serum potassium concentrations than in the healthy control, probably because of the extensive cellular damage produced by the thermal injury (Bush, 1964; Tolmie, Joyce and Mitchell, 1967). For this reason suxamethonium should be avoided in the severely burned patient.

The burned patient may show an increased requirement for non-depolarizing muscle relaxants. This has certainly been reported repeatedly with tubocurarine (Bush, 1964; Martyn et al., 1980), but the phenomenon has proved difficult to explain. Resistance appears not to result from an increased volume of distribution of tubocurarine, or from an increased plasma protein binding, leakage through the burned area or increased renal excretion of the blocker. It is possible that there may be an increased number of acetylcholine receptors at the neuromuscular junction following thermal injury which have an increased affinity for non-depolarizing neuromuscular blocking drugs (Martyn et al., 1982).

Acid–base disturbances

It has long been accepted that respiratory acidosis potentiates the neuromuscular blockade produced by tubocurarine and pancuronium (Baraka, 1964; Norman, Katz and Seed, 1970), whilst respiratory alkalosis had a slight antagonist effect (Payne, 1958). There is more controversy, however, about the effect of metabolic acidosis on the duration of neuromuscular blockade produced by non-depolarizing neuromuscular blocking drugs: it was thought that potentiation could occur in this condition too (Brookes and Feldman, 1962; Bush and Baraka, 1964), but more recently this has been denied (Miller et al., 1978); these workers found more marked potentiation of tubocurarine and pancuronium in conditions of metabolic alkalosis and a similar picture was reported with gallamine in animals (Hughes, 1970).

In a fashion similar to the older agents, the duration of action of vecuronium has also been shown to be increased by respiratory acidosis and reduced by respiratory alkalosis (Gencarelli et al., 1983). Although the breakdown of atracurium is pH dependent, the range of plasma pH is small whatever the disease state, compared with that required to have an effect on the degradation of the drug sufficient to be of clinical significance. Indeed, the clinical significance of any change in acid–base status on the duration of action of a non-depolarizing neuromuscular blocking agent is probably slight.

Electrolyte disturbance

The normal resting membrane potential is dependent primarily on the distribution of potassium ions between the intracellular and extracellular compartments. A reduction in extracellular potassium results in hyperpolarization of the cell membrane and, therefore, a potentiation of neuromuscular blockade. This hyperpolarization would not occur if the intracellular potassium decreased to the same extent. Unfortunately the serum potassium, measured clinically, gives no indication of the changes in trans-membrane potential and Feldman (1963) has suggested that, in chronically depleted states, such as occur with regular diuretic therapy, it is probable that both extracellular and intracellular potassium concentration is reduced and therefore there is minimal effect on neuromuscular blockade. However, Miller and Roderick (1978) have demonstrated potentiation of pancuronium induced paralysis in cats in a state of diuretic-induced potassium depletion. Care must, therefore, be exercised in the use of a non-depolarizing neuromuscular blocking agent in the hypokalaemic patient to avoid a prolonged effect.

Release of acetylcholine from the nerve ending is reduced by an increase in magnesium ion and a reduction in calcium ion concentration and hence these electrolyte changes may well potentiate non-depolarizing neuromuscular blockade (Ghoniem and Long, 1970; Waud and Waud, 1978). This has been demonstrated clinically when magnesium sulphate has been used to treat pre-eclampsia patients (de Silva, 1973).

Hypothermia

In this state, both the degree and duration of block produced by the conventional non-depolarizing neuromuscular blocking agents such as tubocurarine and pancuronium are augmented (Park and MacNamara, 1979) and hypothermia has also been demonstrated markedly to prolong the action of atracurium in patients undergoing cardiac by-pass surgery (Flynn, Hughes and Walton, 1984). This is to be expected, since the spontaneous breakdown of this drug in the plasma is temperature dependent, even within the clinical range of body temperature.

DRUG INTERACTIONS

A wide range of antibiotics is well recognized to potentiate the neuromuscular blockade produced by non-depolarizing neuromuscular blockers. Aminoglycosides, including streptomycin, neomycin, gentamycin and kanamycin were first to be incriminated and have now all been shown to reduce presynaptic quantal release of acetylcholine, although this effect can be reduced by the administration of calcium ions (Rawlins, 1978). Other antibiotics, including the polymyxins, lincosamides and tetracyclines have been shown to have not only pre-junctional, but also post-synaptic effects which, by decreasing the sensitivity of the receptor site to acetylcholine, will potentiate the action of neuromuscular blocking agents (Singh, Marshall and Harvey, 1982). There has even been a suggestion that metronidazole may augment neuromuscular blockade produced by vecuronium, although any such effect is probably of limited clinical significance, as only at exceptionally high concentrations has it been demonstrated that metronidazole may have a weak anticholinesterase effect. Certainly, such interaction has not been demonstrated to occur between metronidazole and pancuronium (McIndewar and Marshall, 1981).

Potentiation of the action of non-depolarizing neuromuscular blocking agents has been reported with a wide range of other drugs. Lithium carbonate has been shown to reduce pre-synaptic release of acetylcholine, especially potentiating the neuromuscular blocking properties of pancuronium in comparison with gallamine and tubocurarine (Hill, Wong and Hodges, 1977). Local anaesthetic agents such as lignocaine and bupivacaine, barbiturates, magnesium and quinidine not only reduce acetylcholine release, but in addition they stabilize the post-synaptic membrane for, by blocking the end-plate ionic channel which opens after acetylcholine has combined with the end-plate receptor, they prevent propagation of the action potential from the end-plate to the muscle fibre and thus potentiate neuromuscular blockade.

Calcium ions are essential for presynaptic release of acetylcholine and it is not surprising, therefore, that prolonged neuromuscular blockade has been reported after the administration of calcium antagonists to treat cardiac arrhythmias in an anaesthetized patient who has received a non-depolarizing neuromuscular blocking drug. The interaction of calcium antagonists and non-depolarizing blockers has recently been reviewed by Jones (1985).

A range of other drugs has been shown in occasional reports to potentiate non-depolarizing neuromuscular blockers. In animal studies, trimetaphan has been shown to enhance the blockade produced by tubocurarine (Deacock and Hargrove, 1962) and it has been suggested that nitroglycerine is able to potentiate the block produced by pancuronium, although the mechanism of action is not clear (Glisson, El-Etr and Lim, 1979).

Diuretics too have been incriminated. Large doses of frusemide (1 mg kg^{-1}) have been shown to potentiate the action of tubocurarine, probably by presynaptic inhibition of transmitter release (Miller, Sohn and Matteo, 1976), although mannitol seems to be free of such side effects.

In contrast, azathioprine and corticosteroids, which are used as immunosuppressants in transplantation surgery, have both been shown to reduce the potency of non-depolarizing myoneural blockers, necessitating the administration of larger doses of the drugs to produce satisfactory paralysis. The mechanism of action of these drugs in this respect is not, however, clear (Vetten, 1973; Hall, 1983), although it is possible that, like theophylline, they facilitate calcium transport across the cell membrane, thus potentiating muscle contraction.

It is also well recognized that the combination of two or more non-depolarizing neuromuscular blockers may produce a prolonged effect either by simple additivity, as with gallamine and tubocurarine and gallamine and pancuronium, or by true potentiation, as with pancuronium and tubocurarine (Waud and Waud, 1985). These effects are probably attributable to the multiple sites for acetylcholine binding on the post-synaptic membrane which the different blockers combine with and compete for to differing extents. The complexity of the effect is such as to suggest that the use of only one non-depolarizing neuromuscular blocker during the course of an anaesthetic is preferable.

Prior administration of a depolarizing agent such as suxamethonium is known to potentiate the duration of action of tubocurarine (Katz et al., 1969) and pancuronium (Katz, 1971), but this effect, although still present, is less marked when vecuronium (Kreig, Hendrickx and Crul, 1981) or atracurium is used (Hunter, Jones and Utting, 1982a).

The interaction between neuromuscular blockers and other drugs has recently been reviewed by Viby-Mogensen (1985).

SUXAMETHONIUM

This is now the only depolarizing neuromuscular blocking agent available in Great Britain and, although it is undoubtedly the drug of choice in some situations, for example when rapid endotracheal intubation is required or difficulty is anticipated, it is certainly not an ideal agent. It has certain side effects which are peculiar to itself and these will be discussed separately in this section.

Muscle pains. Patients commonly complain of aching and painful muscles following administration of the drug (Churchill-Davidson, 1954). The complaint is especially likely to arise in the unpremedicated young patient who is allowed out of bed soon after surgery, although they may occur in virtually any patient. Such pains act as a relative contraindication to the use of the drug, especially in the day case patient. As the likelihood of development of these pains is worsened by repeated doses of the drug, the use of intermittent boluses of suxamethonium must be of limited benefit, especially since the introduction of the shorter acting non-depolarizing agents makes the technique largely obsolete. Symptoms can be very distressing and the patient should be forewarned about them, and told that they may occur in such unexpected sites as the shoulders, the middle of the back and the upper abdomen.

The cause of the muscle pain is unknown and this makes prophylaxis difficult. Small doses of non-depolarizing neuromuscular blocking drugs are frequently used for this purpose and it has been suggested that an adequate interval, of the order of 3 min, must be allowed for significant receptor occupancy to occur after administration of the small dose of tubocurarine or gallamine before suxamethonium is given (Miller and Way, 1971). The efficacy and reliability of suxamethonium is unfortunately reduced when this technique is used and thus a larger dose of depolarizing agent is required. Recent work has suggested, however, that when atracurium and the now obsolete fazadinium are used for this purpose, there is no reduction in the incidence of such pains (Budd et al., 1985). Large doses of thiopentone with lignocaine have been suggested (Haldia, Chatterji and Kackar, 1974), as has pretreatment with benzodiazepines, but a recent report has questioned their efficacy (Chestnutt et al., 1985). Magnesium sulphate, which is known to have post-synaptic neuromuscular blocking properties and theoretically therefore may be of benefit, has also been used to prevent the development of the pains, but unsuccessfully (Chestnutt and Dundee, 1985). In fact, the only drug shown to have any significant beneficial effect is calcium gluconate which, when injected before suxamethonium, decreases both the incidence and the severity of the myalgia, possibly because, by stabilizing cell membranes, it reduces the extent of the increase in serum potassium usually seen after suxamethonium (Shrivastava et al., 1983).

It is interesting to note that the frequency of muscle pains is lower in the pregnant state, possibly because of the neuromuscular blocking properties of progesterone, the plasma concentration of which is increased at this time (Crawford, 1971; Thind and Bryson, 1983).

Prolonged apnoea. Suxamethonium is metabolized in the plasma by the enzyme pseudocholinesterase, usually resulting in 90% recovery of neuromuscular function within 10 min of administration of a 50-mg dose (Hunter, Jones and Utting, 1982a). Inherited abnormalities of the chemical structure of pseudocholinesterase can result in delayed metabolism of suxamethonium, however, and the prolonged apnoea which follows, although not life-threatening, represents a marked but uncommon inconvenience. Artificial ventilation must be adequately maintained in such circumstances and it is also essential to keep the patient anaesthetized throughout the apnoeic period.

Several different genetic defects cause the action of suxamethonium to be prolonged, because the serum cholinesterase enzyme is polymorphic in nature. The molecular structure is determined by several different genes, abnormalities of which can produce an abnormal chemical structure of pseudocholinesterase. Phenotyping, that is the determination of any abnormality produced by the different genes, is based on the inhibition of activity of pseudocholinesterase by different substances, such as cinchocaine, fluoride, chloride and suxamethonium itself. The genes responsible are known as the normal (E_1^u) or usual, atypical (E_1^a), fluoride-resistant (E_1^f) and silent (E_1^s) gene, respectively. Inheritance of these genes is autosomal in nature, with heterozygote patients manifesting less sensitivity to suxamethonium than homozygotes. Thus approximately 94% of the population are homozygote for the normal genes (E_1^u, E_1^u), 4% are atypical heterozygotes (E_1^u, E_1^a) in whom suxamethonium 50 mg would last approximately 30 min and less than 2% of the population have one of the other heterozygote or homozygote abnormalities which result in prolongation of the action of the drug, of which being heterozygote for the fluoride (E_1^u, E_1^f) or silent gene (E_1^u, E_1^s) are the most common (Lim and Churchill-Davidson, 1981).

Non-inherited (acquired) factors can result in low plasma concentrations of pseudocholinesterase of normal molecular structure; for example, this occurs in pregnancy and the puerperium. Indeed, it may take as long as 6 weeks after delivery for the plasma concentrations of pseudocholinesterase to return to normal, although this is probably exceptional, a return usually occurring within 2 weeks (Whittaker and Selwyn-Crawford, 1983). Reduced concentrations have also been reported in chronic liver disease, malignancy, burns, hypothyroidism, blood dyscrasias and renal failure and such factors are thought to account for up to 17% of cases of prolonged apnoea (Bauld et al., 1974). The problem has been reviewed by Lim and Churchill-Davidson (1981).

Several drugs may also interfere with the activity of serum cholinesterase; these include amethocaine, phenothiazines, ketamine, oral contraceptives, propanidid, and trimetaphan in addition to the often quoted, but now rarely used ecothiopate iodide eye drops. Tetrahydroaminoacrine (tacrine) and hexafluorenium should be mentioned: both inhibit pseudocholinesterase and were once used deliberately to prolong the action of suxamethonium, but this technique is now obsolete. It should be added that, whether the cause of the prolonged apnoea is an inherited or acquired defect in the plasma cholinesterase, there is little evidence to suggest that administration of fresh frozen plasma which contains some cholinesterase, is of any practical benefit.

Increased intraocular and intracranial pressure. There is much debate about the degree and duration of the increased intraocular pressure (IOP) produced by suxamethonium, an increase now thought to be explained by sustained contracture of the extraocular muscles which, having a large number of end-plates, respond to suxamethonium in a manner different from other muscle groups which show fasciculations, but similar to the contracture described in avian muscle.

This increase in intraocular pressure can be damaging, especially in the case of a penetrating eye injury, where expulsion of the vitreous humour can ensue. The subject has recently been reviewed by Adams and Salt (1985). Non-depolarizing neuromuscular blocking drugs do not increase the IOP and are therefore less damaging to the open eye, but in patients with a full stomach requiring emergency surgery suxamethonium may still be the safest drug. It is important to note that the effect of endotracheal intubation in increasing the IOP in an incompletely paralysed patient can be much greater than that produced by suxamethonium (Wynands and Crowell, 1960).

The effect of suxamethonium on intra-cranial pressure (ICP) is less clear: some studies have demonstrated an increased ICP after the drug was administered (Marsh et al., 1980), but others have not (Bormann et al., 1980). Although non-depolarizing neuromuscular blocking drugs do not increase ICP directly, the tachycardia produced by gallamine and pancuronium may have adverse effects on intracranial vascular pathology. Furthermore, the potent histamine releasing properties of tubocurarine may produce cerebral vasodilatation. Thus suxamethonium may not be contraindicated if blocking agents are required. Atracurium has been shown to have little effect on ICP in patients with a cerebral tumour (Minton et al., 1985). This subject has recently been reviewed by Murphy (1985).

Increased intragastric pressure. This occurs during the voluntary muscle fasciculations which follow the administration of suxamethonium, pressures of up to 40 mm Hg being recorded. However, as the lower oesophageal sphincter pressures have also been shown to increase to an even greater extent at this time, the risk of regurgitation is probably reduced. This subject has been reviewed by Smith, Dalling and Williams (1978).

Hyperkalaemia. Injection of suxamethonium 1 mg kg^{-1} in humans increases the serum potassium concentration by approximately 0.5 mmol litre^{-1} (Paton, 1959). In patients with an already increased serum potassium concentration, such as those in renal failure, the administration of this drug may therefore precipitate life-threatening cardiac arrhythmias. In addition to the hyperkalaemia caused by suxamethonium in patients with muscle disorders, to which reference has already been made, marked hyperkalaemia has also been reported to occur following suxamethonium in a range of neurological disorders in which muscle denervation and atrophy occurs. These include hemiplegia, following diffuse head injury, encephalitis, ruptured cerebral aneurysm, tetanus and paraplegia (Azar, 1984) and, as has been mentioned previously, in burned patients.

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ADVERSE EFFECTS OF OPIOID ANALGESIC DRUGS

D. J. R. DUTHIE AND W. S. NIMMO

An "opioid" is a drug with morphine-like actions. It may reproduce some of the effects of the endogenous peptides, enkephalins, endorphins and dynorphins, which occur naturally in the central nervous system, and act through multiple receptors. The desired clinical effects are usually relief of pain and diarrhoea or suppression of cough. Opioid antagonist drugs bind receptors without producing an effect. There are partial agonists and opioid agonist/antagonist drugs which, as their name suggests, have intermediate effects.

All opioids share the side effects of respiratory depression, cough suppression, reduced intestinal motility, nausea, vomiting and urinary retention. Tolerance to their effects and both physical and psychological dependence may develop. Hypersensitivity reactions have been reported rarely after i.v. injection. Teratogenic and carcinogenic effects have not been described.

EPIDEMIOLOGY OF THE USE OF OPIOIDS

Opioid analgesics are used widely in hospital practice. In the Boston Collaborative Drug Surveillance Program, 29.7% of 39946 patients in hospital received at least one opioid analgesic preparation. In a study of 628 patients made over 6 months in 15 intensive care units, sedative and analgesic drugs were prescribed more frequently than any other groups of drugs (Farina, Levati and Tognoni, 1981). Morphine was prescribed to 35% of 200 critically ill patients, who received an average of seven different drugs (Buchanan and Cane, 1978).

In anaesthesia, opioids are used frequently for premedication, intraoperative and postoperative analgesia. In the Western Infirmary, Glasgow, a computerized anaesthetic record system has been in operation for 6 years (Todd, Duthie and Spence, 1983). From April 1980 to June 1984, records of 64645 anaesthetics reveal that 41% of patients received opioid premedication and 28% were given opioids during operation to supplement anaesthesia. Volatile anaesthetic agents were used in 94% of all anaesthetic procedures recorded.

EXAMPLES OF OPIOID ANALGESIC DRUGS

The British National Formulary lists 12 opioid drugs under "Narcotic and other analgesics for severe pain" and three "Narcotic analgesics for mild to moderate pain" (table I). Naloxone is the only "opioid antagonist for respiratory depression", although naltrexone and nalmefene are available on clinical trial.

PHARMACOLOGICAL EFFECTS

Mechanisms of Action of the Opioid Analgesics

Opioids dull the appreciation of pain without loss of consciousness. The affective response to pain is altered such that the perception of pain may be preserved whilst the threshold of pain tolerance is increased markedly. The sites of action for analgesic effects are located principally in the brainstem and spinal cord. Endogenous sensory control systems are activated to filter sensory inputs at the level of the spinal cord (Jordan, 1984). Other sites may be responsible for the effects that opioids have on mood and the behavioural response to pain.

Opioids act centrally at both pre- and postsynaptic sites. They inhibit selectively the release of excitatory transmitters from terminals of nerves carrying nociceptive stimuli. Neurones are hyperpolarized, which suppresses spontaneous discharge and evoked responses (Duggan and North, 1983). Opioids do not block nerve conduction in primary afferent fibres at concentrations likely to be achieved after systemic adminis-

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tration (Yuge et al., 1985). Opioid receptors have been demonstrated near the dorsal root ganglion (Fields, Emson and Leigh, 1980) and opioids are placed at this site in high concentration by extradural or intrathecal administration. What effect opiods have on afferent neurones at these sites is still unresolved.

Opioid effects are mediated through multiple opioid receptors (Martin et al., 1976) (table II). Drugs may act at more than one opioid receptor, with varying effects. For example, pentazocine is a weak μ antagonist, but a strong κ agonist. Naloxone is an antagonist at both receptors, but has a greater affinity for the μ receptor (Pleuvry, 1983). Subpopulations of receptors have been proposed. Work in isolated animal tissues, such as guineapig myenteric plexus–longitudinal muscle and mouse vas deferens, has provided a wealth of data. These data are sometimes conflicting and difficult to relate to the clinical effects of opioids.

The adverse effects of opioids result either from a direct toxic effect of the drug or from recognized actions mediated through opioid receptors. An opioid with an action specific for one receptor subtype, with an appropriate affinity and receptor binding holds theoretical advantages for specificity of action with reduced side effects.

The opioid antagonists, naloxone, naltrexone and nalmefene are effective in reversing the adverse effects of opioids, but restore acutely the awareness of painful stimuli. Naloxone and naltrexone have no agonist effects when given on their own in clinical doses (McNicholas and Martin, 1984). Nalmefene exhibits a prolonged duration of action, which appears to be dose related (Gal and DiFazio, 1986).

Relationship Between Plasma Concentration and Effects

Steep concentration–effect curves have been demonstrated for pethidine. In 95 observations in nine patients after intra-abdominal or joint surgery, there was only a difference of 50 ng ml^{-1} between the mean plasma pethidine concentration at which severe pain was experienced (410 ng ml^{-1}) and the mean, minimum plasma pethidine concentration at which pain was relieved (460 ng ml^{-1}) (Austin, Stapleton and Mather, 1980a).

Plasma concentrations of opioid which provide effective analgesia after abdominal surgery vary considerably between individuals. The coefficients of variation in minimum effective analgesic concentration were as high as 39% after hysterectomy when pain was relieved by i.m. pethidine (Austin, Stapleton and Mather, 1980a) and 57% after intra-abdominal surgery, relieved by morphine i.v. from a patient controlled analgesia device (Dahlström et al., 1982). Doubts about the accuracy and reproducibility of the available methods for assaying opioids have been expressed (Faulding and Hall, 1984). Analytical errors may explain inconsistencies in the results of pharmacokinetic studies obtained in different laboratories.

TABLE I. *Opioid drugs appearing in the* British National Formulary *(1985)*.

Severe pain	Mild to moderate pain
Morphine	Codeine
Buprenorphine	Dextropropoxyphene
Dextromoramide	Dihydrocodeine
Diamorphine	
Dipipanone	
Levorphanol	
Meptazinol	
Methadone	
Nalbuphine	
Papaveretum	
Pethidine	
Phenazocine	

Although significant, the variation between patients in concentration and effect is slight compared with the pharmacokinetic variation in the plasma concentration obtained from a dose of opioid, by whichever route it is given (Hug, 1984). Following i.m. injection of pethidine 100 mg to 10 patients who had undergone hysterectomy or cholecystectomy, there was a five-fold variation in the peak plasma pethidine concentration measured (240–1210 ng ml^{-1}), and a seven-fold variation in the time taken for the peak concentration to be reached (15 min–1.8 h) (Austin, Stapleton and Mather, 1980b). Morphine 0.15 mg kg^{-1} given i.m. either as premedication or as postoperative analgesia to 41 surgical patients resulted in peak plasma morphine concentrations which varied from 30 to 160 ng ml^{-1} and were achieved between 4 and 60 min after injection (Rigg et al., 1978).

Minimizing the pharmacokinetic variation by constant infusion of opioid to steady state is possible in the time opioids are given after surgery. After two loading infusion rates, i.v. infusion of pethidine 24 mg h^{-1} for 32 h in 10 hysterectomy patients has produced stable plasma pethidine concentrations and excellent pain control

TABLE II. *Opioid receptors*

Receptor	Effect	Agonist	Antagonist
mu, μ	Analgesia (supraspinal) Ventilatory depression Depression of temperature regulation Miosis Euphoria Indifference to the environment Bradycardia Physical dependence (morphine type)	Morphine -partial Buprenorphine	Naloxone Pentazocine Nalbuphine Nalorphine
kappa, κ	Analgesia (spinal) Sedation Miosis ?Respiratory depression Physical dependence (distinct from morphine)	Morphine Pentazocine Butorphanol -partial Nalbuphine Nalorphine	Naloxone
sigma, σ	Dysphoria, delerium Hallucinations Muscle tone Tachycardia Ventilatory stimulation Vasomotor stimulation Mydriasis (not analgesia)	Butorphanol (Nalbuphine) (Nalorphine)	Naloxone
delta, δ	? Respiratory depression	D-Ala, D-Leu-enkephalin (DADL)	Naloxone

(Stapleton, Austin and Mather, 1979). Constant rate opioid infusion avoids the see-saw plasma concentrations of intermittent bolus dosing, during which patients alternate between inadequate analgesia and the side effects of respiratory depression and nausea and vomiting.

However, the marked variation between individuals in both the steady state concentrations a given infusion rate will achieve and the plasma concentration required to relieve pain, mean that the infusion rate of opioid must be tailored to the individual requirements of each patient. The elimination half-lives of opioids vary from 2 to 10 h (Hug, 1984). Altering the setting of an infusion pump will, therefore, not achieve fully the desired effect until five half-lives, 10–55 h, have elapsed. A practical solution may be to provide a safe background of analgesia, by a constant rate of opioid delivery, which may be supplemented when required—for example, during physiotherapy (Duthie, McLaren and Nimmo, 1986).

Adverse Effects

Adverse effects may be classified as: (1) Predictable: a dose-related extension of pharmacological effects; or (2) Unpredictable.

Predictable adverse effects, such as respiratory depression and nausea and vomiting are documented well in the literature. Unpredictable effects have been reported usually as isolated case histories or small, uncontrolled series. Examples of adverse effects according to body system are given below.

Respiratory system

Mechanisms of opioid respiratory depression. The respiratory depressant effects of opioid analgesics are dose related and linked intimately to their analgesic effects. Opioids exert direct depressant effects on the pontine and bulbar brainstem respiratory centres. Patients have to rely on hypoxic drive to stimulate ventilation, similar to patients with chronic obstructive airways disease, whose arterial carbon dioxide tensions are increased persistently above normal (Bewley and Ghodse, 1984).

Increased reliance on hypoxic drive after opioid therapy is illustrated in a case report of one patient who developed respiratory depression requiring assisted ventilation after bilateral carotid endarterectomy and morphine 6 mg i.m. The same dose had been given to the patient before endarterectomy without ill effect. Damage to the nerve or vascular supply to the carotid bodies was considered to be the cause of the increased sensitivity to the respiratory depressant effects of morphine (Lee et al., 1981). The reduced response to hypoxia following carotid endarterectomy may persist for up to 10 months (Wade et al., 1970).

The respiratory stimulant, almitrine, enhances ventilation by an effect on the peripheral chemoreceptors of the aortic and carotid bodies. It has no central effects on the brain stem. The respiratory depressant effects of fentanyl 6.6 μg kg^{-1} i.v. were antagonized in five female patients before surgery by almitrine 0.5 mg i.v. Tidal volume, respiratory rate and expired minute volume were all reduced significantly in five control patients who received fentanyl alone. There were no significant changes in tidal volume and respiratory rate in the five patients who were given fentanyl and almitrine. Expired minute volume did decrease in these patients, but by half as much as in those who received fentanyl alone (Gaudy, Dauthier and Fourgeaux, 1982).

Pain is an effective antagonist to the respiratory depressant effects of opioids. Abolition of pain by cervical anterolateral cordotomy (Wells, Lipton and Lahuerta, 1984) or neural blockade (Hanks, Twycross and Lloyd, 1981) in patients treated with opioids for painful conditions has been followed by respiratory depression as a result of persisting unopposed opioid action.

Measurement of respiratory depression. The effects of drugs on respiration have been quantified by measurement of the stimulus to ventilation provided by an increased partial pressure of carbon dioxide in inspired gas. The results are plotted to give alveolar ventilation–alveolar P_{CO_2} response curves. An increased or decreased threshold of the respiratory centre to carbon dioxide is represented by parallel displacement of the response curve to the right or left respectively. The gradient of the response curve is related directly to the sensitivity of the respiratory centre to carbon dioxide (Read, 1967). The respiratory pattern following opioid administration is often irregular. Breathing rate must be measured over at least 1 min in order to avoid inaccuracies from sampling errors in a respiratory pattern resembling Cheynes–Stokes breathing.

Airway occlusion pressures in response to carbon dioxide stimulation are increased when patients experience pain. After extradural morphine, airway occlusion pressures are reduced, but not below control measurements made before anaesthesia and surgery. Supporting patients in a 45° elevated position makes no difference to occlusion pressures measured in the postoperative period (Molke Jensen et al., 1984).

Morphine 10 mg and phenoperidine 1.5 mg reduced expired minute volume by 20–35% but, concurrently, reduced oxygen consumption by 20–30%. Minute volume changed in response to both drug action and metabolic requirements (Jennett, Barker and Forrest, 1968). Arterial or end-tidal carbon dioxide tensions must therefore be measured to determine the adequacy of ventilation in relation to carbon dioxide production (Jordan, 1982).

Clinical examples of opioid respiratory effects. In 17 surgical patients morphine 0.15 mg kg^{-1} i.m. before surgery caused a significant increase in mixed venous carbon dioxide tensions and displaced the carbon dioxide response curve to the right. These changes correlated poorly with plasma morphine concentrations (Rigg, 1978).

Although the analgesic and ventilatory effects of opioid partial agonist drugs are related, the maximal effects of these drugs are less than those of pure agonists. Excessive doses of pentazocine, butorphanol, buprenorphine and nalbuphine cause moderately severe respiratory depression unlike the apnoea that is produced by pure agonists (Bellville and Green, 1965; Heel et al., 1978, 1979; Romagnoli and Keats, 1980). In 23 volunteers, nalbuphine 30 mg produced respiratory depression similar to that from morphine 20 mg. However, the dose–response curve for respiratory depression was flatter for nalbuphine than for morphine. Increasing the dose of nalbuphine to 60 mg produced respiratory depression no greater than that produced by nalbuphine 30 mg (Romagnoli and Keats, 1980). This "ceiling effect" for respiratory depression with nalbuphine has been demonstrated for another opioid partial agonist, nalorphine (Keats and Telford, 1966).

Opioid partial agonists have been used to antagonize the respiratory depression caused by pure opioid agonists. Large doses of pure agonists are used during anaesthesia to take advantage of the cardiovascular stability of these drugs. Partial agonists are then used instead of pure antagonists to antagonize respiratory depression, but not analgesia. For example, increments of nalbuphine up to 150 μg kg^{-1} were effective initially in reversing respiratory depression in patients who had received fentanyl 90–120 μg kg^{-1} during anaesthesia, but some recurrent respiratory depression did occur (Moldenhauer et al., 1985). In 53 elderly orthopaedic patients, pentazocine was effective in reversing respiratory depression from fentanyl without any further important side effects (Rifat, 1972).

Respiratory depression occurs after extradural injection of opioids, but may be delayed some hours (Hammond, 1984). In 1200 patients receiving extradural morphine 2 mg in saline 10 ml there was only one report of respiratory depression, which was antagonized on two occasions by naloxone 0.2 mg i.v. without loss of analgesia. A second dose of extradural morphine elicited no respiratory depression in this patient (Reitz and Westberg, 1980). Respiratory depression by extradural opioids may be antagonized by opioid partial agonists in addition to pure antagonists. Nalbuphine has reversed delayed respiratory depression after extradural diamorphine without return of pain (Hammond, 1984). The duration of analgesia provided by extradural opioids is said be dose related. However, a morbidly obese patient who received an accidental overdose of extradural morphine did not develop respiratory difficulties. She received two doses of morphine 50 mg, which provided analgesia for only 10 and 23 h respectively (Robinson, 1984).

The respiratory depressant effects of opioids are antagonized by both opioid antagonists and physostigmine. Physostigmine preserves the analgesic action of opioids and is effective after systemic opioid administration (Weinstock et al., 1982; Snir-Mor et al., 1983).

Cough suppression. Codeine is an effective cough suppressant and is prescribed for this effect when constant coughing serves no useful purpose, is irritating and prevents sleep. Codeine has a low affinity for opioid receptors and its analgesic properties may depend on prior conversion to morphine. The potent antitussive actions of codeine have prompted suggestions that there are opioid receptors which mediate cough suppression, distinct from receptors mediating analgesia and for which codeine has a high affinity.

Cough suppression is a side effect common to all opioid analgesics. It impairs the clearing of sputum and inhaled secretions effectively from the lungs and predisposes to pulmonary infection (Jaffe and Martin, 1985).

Cardiovascular system

Histamine release. Following opioid administration, orthostatic hypotension may occur, especially with hypovolaemia, by direct and indirect mechanisms (Lowenstein, Whiting and Bitter, 1972). Venous capacitance may be increased directly (Hsu, Hickey and Forbes, 1979) whereas, indirectly, histamine release is implicated with morphine and pethidine, but not after methadone and fentanyl (Gardocki and Yelnosky, 1964; Thompson and Walton, 1966). The cardiovascular effects of fentanyl are less than morphine, even in patients with severe cardiac disease (Stanley and Webster, 1978).

Histamine released by opioid drugs is associated with pruritis, urticaria, hypotension and a decrease in systemic vascular resistance (Philbin et al., 1981). In human mast cells derived from skin, morphine, in concentrations of 1.5×10^{-4} and 5×10^{-4} mol $litre^{-1}$ was responsible for the release of histamine *in vitro*. Calcium 1–4 mmol $litre^{-1}$ was necessary for histamine release, which increased with increasing morphine concentration up to a maximum at morphine 5×10^{-4} mol $litre^{-1}$. No histamine release was demonstrable in basophils and the opioid oxymorphone, chemically similar to morphine, produced no such effect (Hermens et al., 1985).

In 45 surgical patients, histamine release was four times as likely in patients given pethidine 4.3 mg kg^{-1} than in those given morphine 0.6 mg kg^{-1}. The newer synthetic opioids, fentanyl and sufentanil, had no such effect, which may explain the cardiovascular stability of these drugs (Flacke, Van Etten and Flacke, 1983). In eight patients before cardiopulmonary bypass, morphine 1 mg kg^{-1} increased mean plasma histamine concentrations seven-fold and was associated with an average reduction in mean arterial pressure of 27 mm Hg and a 42% reduction in systemic vascular resistance. The decrease in systemic vascular resistance correlated well with the plasma histamine concentration. Seven other patients given fentanyl 50 μg kg^{-1} demonstrated no change in plasma histamine concentration and no reduction in mean arterial pressure or systemic vascular resistance (Rosow et al., 1982).

Clinically, the effects of histamine release by morphine were antagonized by a combination of H_1- and H_2-receptor antagonists such as diphenhydramine and cimetidine, without obtunding the increase in plasma histamine concentrations. On their own, they offered little protection to the decrease in systemic vascular resistance and diastolic pressure and increase in cardiac index associated with marked increases in plasma histamine concentrations (Philbin et al., 1981). Naloxone does not stimulate histamine release from mast cells *in vitro* and does not inhibit histamine release produced by morphine. There is no increase in lactate dehydrogenase associated with histamine release from mast cells (Hermens et al., 1985).

Histamine release, therefore, is considered to be a displacement reaction, related to the dose and molar concentration of morphine or pethidine and not a non-specific effect of opioids, related to analgesic potency. It is not determined by opioid receptor binding and is not related to cell membrane damage.

Response to intubation. Analgesic doses of opioid drugs in normovolaemic patients with adequate cardiac function are unlikely to affect the cardiovascular system adversely. One cardiovascular effect of benefit to the anaesthetist is the attenuation of the pressor response to tracheal intubation. Fentanyl 3 μg kg^{-1} i.v. before induction of anaesthesia is sufficient to prevent increases in systemic arterial pressure and heart rate during tracheal intubation in geriatric patients (Chung and Evans, 1985).

Indirect effects may occur via the sympathetic nervous system. Small doses of opioids are associated with increased plasma concentrations of adrenaline and noradrenaline, which increase heart rate and arterial pressure. This response is accompanied by increases in blood glucose and antidiuretic hormone concentrations (Hasbrouck, 1970). Such plasma catecholamine changes are not seen with the high doses of opioids used in anaesthesia for cardiac surgery (Stanley et al., 1980).

Vagus nerve. Opioids may exert effects via the vagus nerve (Reitan et al., 1978). Pethidine has been implicated when heart block developed in a patient with an inferior myocardial infarct (Gershengorn and Haft, 1972). In rabbits, propoxyphene and norpropoxyphene prolong atrioventricular conduction and slow heart rate (Lund-Jacobson, 1978). The same effect with morphine is disputed. In a survey of 154 patients with proven myocardial infarction who received morphine, the four sustained hypotensive episodes which occurred were considered to result from an inappropriate heart rate in response to a reduction in arterial pressure and not from a primary conduction defect. These episodes followed first administration of morphine and were not apparent with repeat doses. There was no association with inferior myocardial infarction (Semenkovich and Jaffe, 1985). Direct chronotropic and inotropic effects are not important in doses of opioids used clinically (Eckenhoff and Oech, 1960).

Opioid antagonists. Naloxone can cause hypertension, pulmonary oedema and ventricular fibrillation when given to antagonize the effects of opioids (Tanaka, 1974; Flacke, Flacke and Williams, 1977; Azar and Turndorf, 1979; Cuss, Colac,o and Baron, 1984; Prough et al., 1984). Although found usually in patients with pre-existing cardiopulmonary disease, cardiac arrest has been reported in previously healthy patients (Andree, 1980), as has pulmonary oedema, even when naloxone was given i.v. in small increments (Taff, 1983). It is not clear if these are drug effects or if they result from the experience of severe pain.

Naloxone may partially antagonize the hypotension associated with shock of varied aetiology, possibly by antagonism of the effects of endogenous opioids (Holaday, 1983). No changes in arterial pressure are seen when normotensive and hypertensive subjects are given clinical doses of naloxone (Estilo and Cottrell, 1982), but hypertension has been induced in a patient given a total of naloxone 26 mg i.v. over 2.5 h. This hypertension was antagonized by concurrent administration of clonidine, which produced profound hypotension when given alone (Levin et al., 1985).

Miscellaneous. Gangrene has been produced by accidental i.a. injection of pethidine, pentazocine, diamorphine and dextropropoxyphene. Arterial injection of crushed codeine tablets has caused gangrene, but it was the microcrystalline cellulose, not codeine which was the responsible ingredient. This ingredient is present in formulations of oral methadone, oxycodone, paracetamol, aspirin with codeine and dextropropoxyphene (Goldberg, Bahar and Yosipovitch, 1984).

Gastrointestinal system

Gastro–oesophageal reflux. Decreased lower oesophageal pressure has been demonstrated in 35 volunteers given doses of opioids i.v., just sufficient to induce drowsiness. Morphine 7–10 mg and pethidine 40–50 mg decreased lower oesophageal pressure and increased the severity of reflux in those with pre-existing spontaneous oesophageal reflux (Hall et al., 1975). Similar effects were produced in volunteers by pethidine 1–3 mg (Hey et al., 1981). By decreasing lower oesophageal pressure, opioid drugs make regurgitation and aspiration of gastric contents more likely (Cotton and Smith, 1984).

Gastric emptying and intestinal transit. Opioids reduce gastrointestinal motility with an increase in tone in the gastric antrum and the first part of the duodenum. Longitudinal propulsive peristalsis is reduced, whereas contractility and sphincter tone are increased.

Ileus after surgery results from neurogenic inhibition of gastrointestinal motility mediated by non-cholinergic, non-adrenergic vagal inhibition of the stomach and sympathetic inhibition throughout the gastrointestinal tract (Lisander and Stenqvist, 1985). Systemic opioid drugs may aggravate postoperative ileus by constricting smooth muscle, delaying gastrointestinal transit, and inhibiting gastric emptying (Nimmo, Wilson and Prescott, 1975; Nimmo et al., 1975).

Gastric emptying in seven patients, measured 24 h after hysterectomy, was significantly reduced by diamorphine 5 mg i.m. given every 6 h to relieve pain. Gastric emptying was assessed by measurement of the rate of paracetamol absorption following oral administration of the drug. There was little difference from normal in gastric emptying when the patients' pain was relieved by extradural lignocaine (Nimmo et al., 1978). In 30 chloralose anaesthetized cats, extradural fentanyl counteracted sympathetic inhibition of gastrointestinal motility, assessed by measurement of gastric volume. This effect was reversed by extradural naloxone and not reproduced by i.v. fentanyl (Lisander and Stenqvist, 1985). Both avoiding systemic opioid drugs and relieving the sympathetic inhibition of gastrointestinal motility appear to be effective in minimizing ileus after surgery.

Naloxone antagonizes opioid–induced delay in gastric emptying and drug absorption, but can itself affect gastric motility. Naloxone 2 mg delayed gastric emptying of solids in healthy volunteers (Champion et al., 1982).

Decreased colonic motility as a result of opioids causes desiccated faeces and constipation. This is reversed by naloxone, but analgesia is forfeited. By diminishing intestinal secretion and peristaltic activity, opioids are effective antidiarrhoeal agents (Awouters, Niemegeers and Janssen, 1983).

Constipation may be prevented by anthraquinone cathartics (senna, cascara, danthron and aloe). These drugs must undergo transformation in the colon to active metabolites and therefore are effective on the distal colon only (Hardcastle and Wilkins, 1970). They act directly on the wall of the colon to stimulate longitudinal peristalsis. A dose of 3.75 mg of total sennosides is effective in reversing the constipation produced by codeine 60 mg or its equivalent (Maguire, Yon and Miller, 1981).

Gastrointestinal secretions. Opioids reduce gastric, biliary and pancreatic secretions and can inhibit secretions provoked by secretagogues such as prostaglandin E2 (Turnberg, 1983). The volume and pH of gastric contents of surgical patients, when aspirated immediately after tracheal intubation, were no different 2 h after oral naloxone or placebo (Molke Jensen, Thiessen and Christensen, 1986).

Together, these effects can cause symptoms of abdominal pain, vomiting, weight loss and apparent intestinal obstruction after repeated opioid administration (Sandgren, McPhee and Greenberger, 1984). Clonidine is effective in alleviating such symptoms by enhancing intestinal motility (Lechin and van der Dijs, 1983) and promoting fluid and electrolyte absorption (McArthur et al., 1982).

Blood flow. The effects opioids have on gastrointestinal blood flow vary according to the drug and the dose at which it is given. In dogs, fentanyl demonstrates a dose-dependent decrease in intestinal vascular resistance, an increase in flow and a decrease in oxygen uptake. The net effect is an increase in hepatic oxygen supply. Morphine 1 mg kg^{-1} produced no change in total intestinal blood flow, but the proportion directed through nutritive exchange vessels increased, possibly as a result of histamine release. At five times this dose, morphine increased vascular resistance mediated by adrenaline released from the adrenal gland (Tverskoy et al., 1983).

Entero–systemic circulation of opioids. Secondary peaks are seen often in plasma concentration–time graphs during pharmacokinetic studies of the more lipid soluble opioids. Increased plasma concentrations long after opioid administration has ceased may explain reports of delayed respiratory depression associated with opioids (Adams and Pybus, 1978; Sebel et al., 1984). Controversy exists over whether or not this results from absorption of opioid, first sequestered in the acidic gastric juices then absorbed from the small intestine. Opioid drugs are subjected to a high first pass clearance from the gastrointestinal tract, which must be overcome for entero–systemic circulation to affect plasma concentrations. In dogs, gastric sequestration of fentanyl has been demonstrated, but a small fraction only of the dose administered appeared in the stomach. Hepatic extraction failed to prevent recirculation, but the dose of fentanyl was 100 $\mu g\ kg^{-1}$ (Clark et al., 1985).

Liver and biliary system

Hepatocellular damage. Increased plasma liver enzyme concentrations and centrilobular hepatic necrosis have been demonstrated in spontaneously breathing mice and rats after subanaesthetic doses of fentanyl. These changes are similar to those seen with volatile anaesthetic agents under the same conditions (Baden et al., 1985). Liver damage increases with increasing doses of fentanyl in hypoxic rats (Shingu et al., 1983). It occurs with small doses of fentanyl injected to the cerebral ventricles and is prevented by simultaneous naloxone administration (Needham et al., 1981). The mechanism proposed is liver hypoxia rather than a direct toxic effect (Shingu et al., 1983). Increases in liver enzyme concentrations were the same for cirrhotic and non-cirrhotic animals (Baden et al., 1985).

In dogs, fentanyl improved intestinal blood flow and decreased oxygen uptake, improving liver oxygen supply. However, the lungs of these dogs were ventilated artificially (Tverskoy et al., 1985). The conflicting findings of hypoxic liver damage and improved hepatic oxygenation, both attributed to fentanyl, may result from a species difference or the prevention of hypoxia by artifical ventilation of the lungs.

Biliary function. The tone of the choledochoduodenal sphincter is increased by opioid analgesics. Opioid premedication in patients with biliary disease may cause sphincter pain severe enough to mimic acute cholecystitis or myocardial infarction (Lang and Pilon, 1980). Opioid drugs have been held responsible for preventing contrast medium reaching the duodenum during cholangiography (McCammon et al., 1978). However, in doses used during balanced anaesthesia, only 3% of abnormal cholangiograms were attributable to the anaesthetic technique (Jones et al., 1981). In two groups of 112 patients undergoing cholecystectomy either with or without a fentanyl supplement, only three patients, drawn from both groups, demonstrated sphincter spasm (Chisolm et al., 1983).

Pentazocine, unlike tramadol and buprenorphine, increases intrabiliary pressure and prolongs sphincter closure time, thus reducing bile flow through the ampulla of Vater (Staritz et al., 1985). The partial agonists nalbuphine and butorphanol decrease biliary flow rate and increase intrabiliary pressure less than morphine (McCammon, Stoelting and Madura, 1984). Naloxone and glucagon (Jones, Fiddian-Green and Knight, 1980) reverse the effects of opioids on the choledochoduodenal sphincter.

Central nervous system

Tolerance and dependence. Tolerance to the analgesic effects of opioid analgesics, and their ability to induce physical and psychological dependence is well known (Jaffe and Martin, 1985). In the clinical use of opioids during anaesthesia and for the relief of pain after surgery, reports of acute tolerance and dependence to opioid analgesics are rare. In the Boston Collaborative Drug Surveillance Program, dependence was documented in only four of 11882 patients who received an opioid analgesic drug and had no previous history of addiction (Porter and Jick, 1980). Hydromorphone, percodan and pethidine (twice) were the opioids responsible in these four cases of dependence, only one of which was considered "major".

Acute tolerance to methadone was proposed when patients, who underwent orthopaedic surgery under local anaesthetic extradural blockade, demanded more methadone i.v. after surgery than others, who had received methadone during the procedure as part of a balanced anaesthetic technique (Porter et al., 1983). Patients after cholecystectomy who received morphine by infusion for 24 h to provide a background of analgesia, demanded more morphine i.m. in the subsequent 24 h than those given a placebo infusion (Marshall et al., 1985). Animal studies have demonstrated that acute tolerance to fentanyl develops when opioids are given without painful stimuli, but not when pain is experienced at the time of opioid administration (Colpaert et al., 1980).

Patients anticipate pain after surgery and vary greatly in their analgesic requirements. Patients whose pain is treated effectively immediately after surgery by neural blockade or opioid infusion may be dissatisfied with a subsequent inferior analgesic regimen. Whether the greater demands for opioids reported in certain groups of patients resulted from acute tolerance to opioids or a greater expectation of success from analgesic therapy is unresolved.

Cerebral toxicity. Pethidine therapy can cause excitatory toxic effects in the central nervous system. Jitteriness, tremors, myoclonus and convulsions occur in progression proportional to the plasma concentration of norpethidine, an active metabolite of pethidine (Goetting and Thirman, 1985). Electroencephalographic (EEG) changes of slow wave activity and epileptiform discharges resolve when norpethidine is excreted, unless an underlying cause for seizures persists (Kaiko et al., 1983).

After therapeutic doses, high voltage, low frequency changes are seen in the electroencephalogram, as occur during natural sleep. At the high doses of opioids used in opiate anaesthesia for cardiac surgery, marked EEG effects are apparent. Fentanyl 30–70 $\mu g\ kg^{-1}$ and sufentanil 15 $\mu g\ kg^{-1}$ produce massive increases in the delta power of the EEG, when analysed by computerized three-dimensional power spectral analysis. High voltage, slow delta waves of 0.5–2.5 Hz were characteristic and the total power decreased with time. Although isolated sharp wave activity was seen over the frontotemporal region initially, no other excitatory activity was apparent (Sebel et al., 1981; Bovill et al., 1982). The effects of high dose opioids are depressive predominantly.

The pharmacokinetics of pethidine influence its cerebral toxicity. Pethidine undergoes extensive first pass metabolism when given orally (Mather and Tucker, 1976). An oral dose produces lower plasma concentrations of pethidine and higher concentrations of norpethidine than the same dose given parenterally (Stambaugh, Wainer and Stanstead, 1976). Norpethidine is cleared from plasma by the kidney. The oral route and renal impairment both increase the susceptibility of patients to cerebral toxicity from pethidine by increasing plasma concentrations of norpethidine (Kaiko et al., 1983).

Perceptual disturbances occur in 7–10% of patients taking pentazocine. Visual hallucinations are more common than auditory and reaction to these experiences varies from pleasure to intense dislike (Wood et al., 1974).

Opioids affect motor function by central actions. Methadone can induce choreic movements of the upper limbs and torso and disordered speech. An interaction between methadone and opioid receptors is thought to influence the release of neurotransmitters such as dopamine, in the brain (Wasserman and Yahr, 1980). These effects resolved once methadone was withdrawn. More than 12 mg of extradural morphine in a day may cause opisthotonos, rigidity, spasticity and miosis, which is antagonized by naloxone, and does not affect cardiovascular and respiratory function (Engquist, Chraemmer-Jørgensen and Andersen, 1980).

Depression of conscious level by opioids is reversible by both opioid antagonists and physostigmine. Physostigmine has the advantage of maintaining the analgesic effects of opioids whilst restoring consciousness. It is effective after both systemic (Weinstock et al., 1982) and extradural (Schulman, Sandler and Brebner, 1984) opioid administration.

Nausea and vomiting. All opioids used clinically produce nausea and vomiting by direct stimulation of the chemoreceptor trigger zone in the area postrema of the medulla. The effect is dose-related and tolerance to it develops rapidly. Nausea and vomiting are frequent despite opioids having also a depressant effect on the vomiting centre (Clark, 1984). The emetic effect of morphine may be treated by anticholinergics and phenothiazines, especially those which are antagonists at dopamine receptors (Jaffe and Martin, 1985).

Morphine as premedication increased the incidence of nausea, retching and vomiting in patients undergoing uterine curettage from 22% in controls to 65%. When morphine was combined with atropine the incidence was 35% (Riding, 1960). A biphasic dose–response curve has been proposed for the effect pethidine has on nausea and vomiting (Bellville, 1961). Premedication with pethidine less than 1 mg kg^{-1} i.m. was associated with an antiemetic effect, whereas at doses greater than 1 mg kg^{-1}, pethidine caused nausea and vomiting.

Stimulation of the vestibular apparatus is a potent cause of nausea and vomiting during opioid therapy. Walking, sitting up in bed and turning the head to follow a conversation are sufficient to provoke vomiting (Rubin and Winston, 1950). Pain itself can elicit nausea and vomiting. In a survey of 104 patients undergoing abdominal surgery, 59% of patients suffered concomitant pain and nausea, whereas nausea was provoked by only 3.4% of morphine injections (Andersen and Krohg, 1976).

Not only are nausea, vomiting and retching unpleasant and likely to be painful for patients with surgical wounds, but aspiration into the lungs of vomited gastric contents may be fatal (Brahams, 1984).

Pupillary effects. Most opioid agonists at μ and κ receptors cause constriction of the pupil by stimulation of the Edinger–Westphal nucleus of the third cranial nerve. Pinpoint pupils are pathognomonic of opioid toxicity until hypoxia supervenes and mydriasis develops (Jaffe and Martin, 1985).

Genitourinary system

Opioid analgesics cause an increase in urinary sphincter pressure and a decrease in central inhibition of detrusor tone (Doyle and Briscoe, 1976). Retention of urine is a frequent finding with opioids after extradural, i.m. (Petersen et al., 1982) and sublingual (Murray, 1983) administration. In 56 patients whose pain after upper abdominal surgery was relieved by i.m. or two regimens of extradural morphine, the incidence of acute retention of urine within the first 24 h was 35%, 33% and 50% respectively. These differences were not significant, but patients received two to three times the dose of morphine by the i.m. route than by the extradural route during the first 24 h after surgery (Petersen et al., 1982). Naloxone antagonizes these effects, promoting an increase in detrusor contractility with a reduction in functional bladder capacity (Murray and Feneley, 1982).

The influence of opioids on the autonomic control of bladder function may be mediated through opioid receptors found on neurones within the thoracic spinal cord (Murray, 1984). The site of maximum pressure in the urethra of males with prostatic hypertrophy is within the prostatic urethra. The bladder neck is not closed and the external sphincter is inhibited. All these findings are altered by bladder decompression and blockade of sympathetic alpha adrenoceptors (Cain and Perlberg, 1977). Phenoxybenzamine is effective in preventing urinary retention in women, who have had pain after Caesarean section relieved by extradural morphine (Evron, Magora and Sadovsky, 1984). Changes in prostatic urethral pressure cannot explain the effects of phenoxybenzamine in women. The proposed site of action of opioids and alpha sympathomimetic antagonists in regulating bladder function is in the thoracic spinal cord, where some preganglionic sympathetic neurone cell bodies are surrounded by terminals containing enkephalins and substance P (Murray, 1984).

Failure to ejaculate after lumbar extradural morphine has been described (Torda et al., 1980). A similar effect has been found in rats after intrathecal morphine. This was reversed by naloxone and was not demonstrated when morphine was given i.p. (Wiesenfeld-Hallin and Södersten, 1984). Opioids may produce this effect by modification of the sympathetic response to sexual stimuli. Extradural opioids may be of use in the treatment of premature ejaculation (Pybus et al., 1984).

Morphine should be used with caution in the harvesting of ova for *in vitro* fertilization. Abnormal fertilization and development of up to 33% of eggs have been demonstrated in *in vitro* fertilization of sea urchin eggs incubated with morphine (Cardasis and Schuel, 1976). No inhibition or abnormal development was demonstrated using fentanyl at concentration at or higher than those to which ova are exposed during balanced anaesthesia (Bruce, Hinckley and Norman, 1985). All opioids enhance the release of prolactin, which may interfere with the subsequent endometrial implantation of the fertilized egg (Watson, 1986).

Endocrine system

Endocrine response to trauma. Injury to the body from surgical or other causes is followed by a recognized endocrine and metabolic response, which is related to the severity of the trauma (Traynor and Hall, 1981). The hormonal changes involved are affected by opioid drugs and in some patients have been prevented by them.

In 28 gynaecology patients undergoing tubal reconstruction, increases in blood glucose, plasma cortisol and growth hormone concentrations seen under balanced anaesthesia were abolished by anaesthesia involving fentanyl 50 μg kg^{-1} (Hall et al., 1978). However, in 30 patients having more major gynaecological surgery, the increase in plasma cortisol concentrations was not obtunded in three groups who received fentanyl 13, 12 and 25 μg kg^{-1}, respectively (McQuay et al., 1979). Similarly, fentanyl 10–15 μg kg^{-1} with a subsequent infusion of mean dose 2.9 μg kg^{-1} h^{-1} was insufficient to prevent hyperglycaemia in 25 patients undergoing repair of abdominal aortic aneurysms (Florence, 1978). The long-term benefits of a high-dose opioid technique remain unproven and the disadvantage of prolonged respiratory depression after surgery make it unsuitable for large numbers of patients.

The release of vasopressin in response to an osmotic challenge of hypertonic saline in fit volunteers was inhibited by an analogue of met-enkephalin. This analogue produced a diuresis in water deprived volunteers, which was attenuated by naloxone (Grossman et al., 1980). Morphine 2 mg kg^{-1}, but not 1 mg kg^{-1}, was effective in preventing a significant increase in plasma antidiuretic hormone concentrations in six patients undergoing cardiac surgery (Philbin and Coggins, 1978). Opioids appear to be able to cause a diuresis by suppression of osmotically mediated release of vasopressin, and prevent antidiuretic secretion in response to surgery.

Adrenal insufficiency. Adrenal insufficiency has been demonstrated in methadone addicts. In five methadone addicts, basal plasma cortisol concentrations were no different from controls, but the cortisol secretion following ACTH 0.25 mg i.m. was blunted. This was attributed to a deficiency in ACTH and β-endorphin secretion in addicts causing secondary hypoadrenalism (Dackis et al., 1982). However, measurement of ACTH concentration in 10 methadone addicts and five others who had been weaned from the drug for over 6 months suggested that adrenal insufficiency resulted from compensated primary hypoadrenalism. Again there were no differences in basal cortisol concentrations between the two groups, but addicts had ACTH concentrations that were 60% higher than ex-addicts. These data suggest that methadone is responsible for an effect in the adrenal cortex and not in ACTH or β-endorphin production (Pullan et al., 1983).

Haemopoietic system

Thrombocytopenia, from a drug-related immunological mechanism, has been described in heroin addicts (Adams et al., 1978). Although the effects of chronic sepsis in these patients cannot be discounted, antiplatelet antibodies have been detected (Fishmann, 1981). Morphine i.m. has caused thrombocytopoenia 7 days after elective surgery. The platelet count returned to normal when morphine was discontinued (Cimo, Hammond and Moake, 1982).

Agranulocytosis has been induced by pentazocine (Marks and Abramson, 1980; Sheehan, Hyland and Norman, 1985). After 4–6 weeks, there was an abrupt onset of rigors and localized infection with a neutropenia, which resolved when pentazocine was discontinued. This pattern is consistent with destruction of leucocytes in the peripheral blood by antibodies generated in response to drug sensitivity (Pisciotta, 1978).

Large doses of fentanyl 50–100 μg kg^{-1} used in anaesthesia for open heart surgery can cause haemolysis. Serum haemoglobin concentrations are significantly greater in patients whose anaesthesia is induced by fentanyl rather than volatile anaesthetic agents. In adult patients, from 70 to more than 100 ml of fentanyl solution 50 μg ml^{-1} are used and this volume of hypotonic solution, injected rapidly, is likely to be responsible (Furuya and Okumura, 1986).

Musculo-skeletal system and skin

Muscle rigidity. Muscular rigidity is induced in all muscle groups by the large doses of opioids used in opioid anaesthesia for cardiac surgery. Morphine 2 mg kg^{-1}, fentanyl 17 μg kg^{-1} and alfentanil 175 μg kg^{-1} have all produced muscle rigidity. There are marked increases in voltage detected by surface electromyographic recordings, but no associated electroencephalographic changes (Sebel et al., 1981; Bovill et al., 1982; Scott and Sarnquist, 1985). Central venous pressure increases and there is resistance to artificial ventilation of the lungs from decreased chest wall compliance and upper airway obstruction. Adduction of the vocal cords and supraglottic obstruction by soft tissues have been suggested as reasons for airway obstruction (Scamman, 1983; Benthuysen et al., 1986). This effect on muscle tone is likely to be a central effect at a site above the spinal cord (Freund et al., 1973). Neuromuscular blocking drugs effectively abolish all muscle tone and are appropriate at induction of anaesthesia.

In case reports of muscular rigidity after initial recovery from anaesthesia, both neuromuscular blocking drugs and naloxone have been used (Christian, Waller and Moldenhauer, 1983; Goldberg et al., 1985). In uncontrolled reports of prompt, successful treatment of life-threatening emergencies, it is less clear whether respiratory depression or muscle rigidity is the problem than when electromyographic monitoring has been available for studies performed at induction of anaesthesia. Because of the adverse haemodynamic effects of acute antagonism of opioid drugs, neuromuscular blocking agents free from hypotensive effects have been advocated as the preferred treatment of opioid-induced muscle rigidity (Wangler and Gupta, 1983).

Histamine release after morphine has been demonstrated in connective tissues but not in basophils (Hermens et al., 1985). It is not an effect common to all opioids, related to analgesic potency, rather an adverse effect of morphine and pethidine.

Pruritis. Facial pruritis following extradural injection of opioids is attributed variously to histamine release, an effect of opioid spreading to the medulla or fourth ventricle, or opioid action in the substantia gelatinosa of the spinal cord, referring pruritis to a distant site by neuronal transmission (Scott and Fischer, 1982a). Three patients had facial pruritis, which arose 2–5 h after spinal morphine or diamorphine 1 mg, relieved without return of pain by naloxone 0.4 mg i.v. These patients suffered no further itching when subsequent intrathecal opiate was given together with 0.25% bupivacaine (Scott and Fischer, 1982b).

Miscellaneous effects. Alopecia areata in the occipital area has been reported in a patient after 3 days of extradural morphine, which was complicated by widespread itching (Andersen, 1984). This was thought not to result from pressure and to be unlike temporary telogen effluvium described 1 month after anaesthesia and surgery (Desai and Roaf, 1984).

Fixed drug reactions from opioids are uncommon, but have occurred with morphine, opium and codeine (Derbes, 1964). Smoking and inhaling vapours of heroin and methaqualone has resulted in macular pigmentation of the tongue (Westerhof et al., 1983).

Repeated, superficial injection of pentazocine has led to sclerosis, inflammatory nodules and ulceration of the skin surrounded by a halo of hyperpigmentation. Precipitation of the acidic pentazocine in alkaline extracellular fluid may initiate this reaction (Schlicher, Zuehlke and Lynch, 1971).

Fibrous myopathy with contractures has developed after repeated i.m. injection of pethidine and pentazocine. This appears at the site of injection and leaves distal muscle groups unaffected (Mastalgia, Gardner-Medwin and Hudgson, 1971; Adams, Horowitz and Sundstrom, 1983).

Hyperkalaemia associated with heroin overdose may occur by ischaemic muscle injury (Pearce and Cox, 1980).

Self poisoning

Accidental and deliberate self poisoning with opioid analgesics is common. Dextropropoxyphene, formulated in combination with paracetamol, is the drug most commonly associated with death after self poisoning (OPCS, 1982). Only 4% of those poisoned required treatment to prevent liver damage from paracetamol poisoning, and a proportion similar to that in self poisoning with paracetamol alone. Death was more likely to be attributable to respiratory depression and sudden cardiovascular collapse, possibly as a result of depression of atrioventricular conduction by dextropropoxyphene (Lund-Jacobson, 1978).

Drug interactions

Opioids exhibit both pharmacodynamic and pharmacokinetic interactions with other drugs. For example, additive effects occur with central nervous system and respiratory depressants and the analgesic effects of methadone are reduced by rifampicin, because of liver enzyme induction (*British National Formulary*, 1985).

Two types of interaction between monoamine oxidase inhibitors and pethidine have been

TABLE III. *Therapeutic indices of opioid analgesics in rats and mice*

Drug	Therapeutic index (LD_{50}/ED_{50})
Sufentanil	25211
Fentanyl	277
Phenoperidine	166
Morphine	69
Pentazocine	31
Pethidine	5

described. The first is characterized by respiratory depression, hypotension and depressed consciousness. It resembles pethidine overdose and is antagonized by naloxone. It may be explained by inhibition of pethidine metabolism by monoamine oxidase inhibitors. The second is an idiosyncratic reaction involving central nervous system excitation, hypertension, tachycardia, pyrexia, rigidity and convulsions. This interaction has not been reported with morphine in man, but has been seen with pethidine, morphine and pentazocine in mice (Rogers and Thornton, 1969).

Diagnostic tests

Therapeutic plasma concentrations of morphine may interfere with the measurement of amylase, lipase, lactate dehydrogenase, creatine phosphokinase in serum or plasma and glucose in urine (Benedicts) (Hansten, 1979).

SUMMARY

Opioids were available in clinical practice since before the birth of modern anaesthesia—Setürner isolated morphine in 1806. They have a record of safety which is reflected in their high therapeutic ratios, especially the synthetic opioids introduced recently (table III). The most serious immediate adverse effect, respiratory depression, is a predictable effect related closely to analgesia. It is fortunate for anaesthetists who use opioids regularly, that recognition and treatment of respiratory problems are an integral part of their craft and that opioid antagonists are effective in reversing respiratory depression.

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Br. J. Anaesth. (1987), 59, 78–95

ADVERSE EFFECTS OF LOCAL ANAESTHETICS

F. REYNOLDS

Local anaesthetics have direct effects at high concentration upon tissues near the site of injection: *local* effects; they have remote effects resulting from nerve conduction blockade: *regional* effects; they produce an odd collection of localized effects resulting from transport of relatively high concentrations by strange routes such as the arterial supply to parts of the brain: these I have termed *focal* effects; and they produce effects at low concentration following absorption into the general circulation: *systemic* effects. Adverse reactions to local anaesthetics may be manifestations of any of these types of effect, a fact which is frequently overlooked.

LOCAL EFFECTS

Local anaesthetics are drugs which *reversibly* block nerve conduction when applied locally in appropriate concentrations, therefore by definition they do not produce irreversible neurological damage. However, the concentration of a local anaesthetic at the site of injection is likely to be 10000 times the systemic concentration, and when from time to time neurological complications do follow regional blockade, the drug itself may be blamed, particularly if it is a relatively new one. Thus every local anaesthetic has been the subject of reports of neurological sequelae following extradural and spinal blockade, including lignocaine (Harrison, 1975), bupivacaine (Cuerdon, Buley and Downing, 1977), etidocaine (Ramanathan et al., 1978) and more recently chloroprocaine (Covino et al., 1980; Ravindran et al., 1980; Reisner, Hochman and Plumer, 1980; Moore et al., 1982).

In the reports such as those cited for bupivacaine and etidocaine above, neural blockade persisted only for a few days, in which case it is plausible to suggest that the drug itself was contributory. Some cases of unexpectedly prolonged neural blockade following delayed extradural spread can be attributed to subdural extra-arachnoid placement (Conklin and van der Wal, 1980; Brindle Smith, Barton and Watt, 1984; Pearson, 1984). There are occasional reports of longer lasting neurological sequelae from apparently correctly conducted spinal anaesthesia (Meeuwis, Soetens and van Zundert, 1980). Where sequelae are permanent, however, and particularly following extradural blockade there are many other, more likely causes such as cord ischaemia. The causative importance of hypotension in this respect is emphasized by the occurrence of paralysis following hypotensive *general* anaesthesia (Costello and Fisher 1983; Schreiner et al., 1983).

Injecting the wrong solution to the extradural space, or an inappropriate formulation to the subarachnoid space, are other clearly avoidable non-local anaesthetic causes of disaster. The possible neurotoxicity of local anaesthetic drugs themselves is the continuing subject of laboratory research, sparked off most recently by problems following the use of chloroprocaine in the United States. The work of Gentili and colleagues (1980) suggested that there was some difference between local anaesthetics in their neurotoxicity following intrafascicular injection in rats, but differences in formulation could have influenced the outcome. Ravindran, Turner and Muller (1982) showed that, following subarachnoid administration in dogs, persistent paralysis followed chloroprocaine, but not bupivacaine or acidified saline. More recently, Li and colleagues (1985) showed that bupivacaine, lignocaine and chloroprocaine all produced equivalent paralysis following subarachnoid infusion in rats, with no significant histological changes, while the findings of Rosen and colleagues (1983) for large volume subarachnoid injections in monkeys and sheep were similar. On the other hand, Seravalli, Lear and Cottrell

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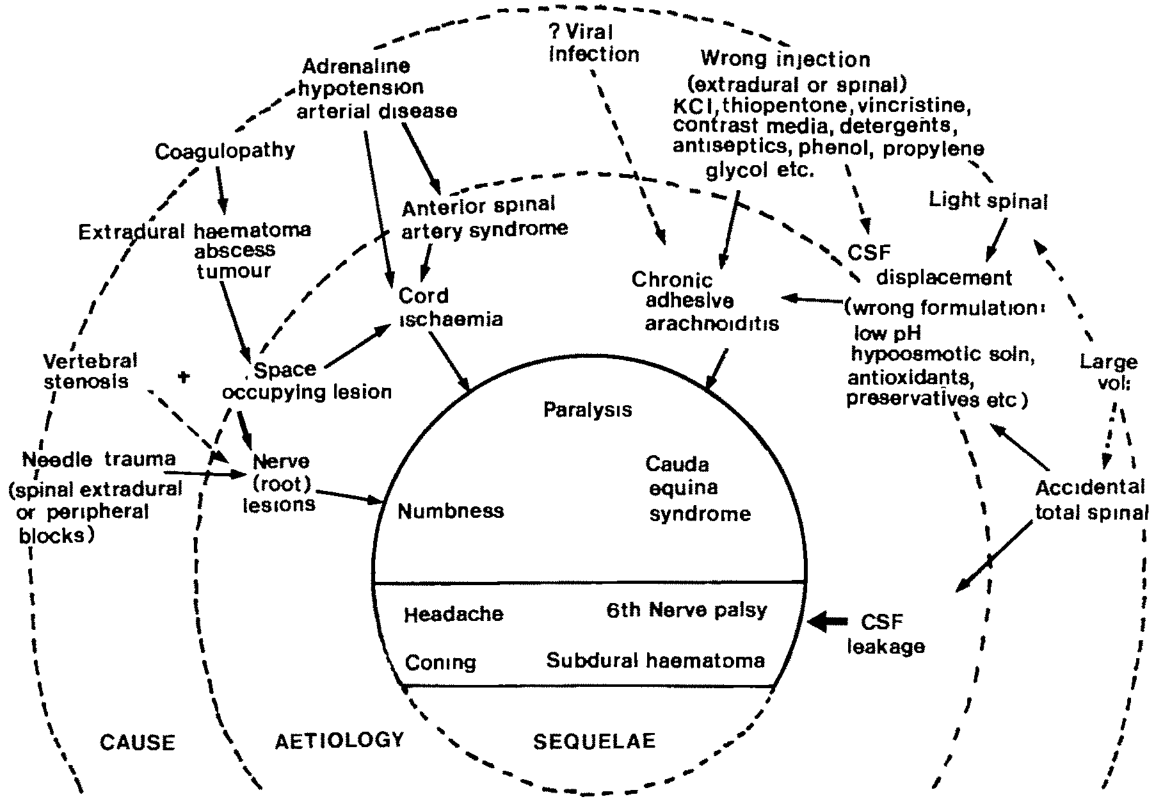
? Viral infection
Adrenaline hypotension arterial disease
Wrong injection (extradural or spinal) KCl, thiopentone, vincristine, contrast media, detergents, antiseptics, phenol, propylene glycol etc.
Coagulopathy
Light spinal
Anterior spinal artery syndrome
Extradural haematoma abscess tumour
CSF displacement (wrong formulation: low pH hypoosmotic soln, antioxidants, preservatives etc)
Chronic adhesive arachnoiditis
Cord ischaemia
Vertebral stenosis
+
Space occupying lesion
Large vol:
Paralysis
Needle trauma (spinal extradural or peripheral blocks)
Nerve (root) lesions
Cauda equina syndrome
Accidental total spinal
Numbness
Headache
6th Nerve palsy
CSF leakage
Coning
Subdural haematoma
CAUSE
AETIOLOGY
SEQUELAE

FIG. 1. Causation of neurological complications following regional (principally spinal and extradural) block. (Data from: Urquhart-Hay, 1969; Usubiaga, 1975; Chaudhri, Kop and Dhruva, 1978; Covino et al., 1980; Gentili et al., 1980; Meeuwis, Soetens and van Zundert, 1980; Reisner, Hochman and Plumer, 1980; Moore et al., 1982; Newrick and Read, 1982; Schimek and Fink, 1982; Newman, 1983; Wang et al., 1984; Rendell-Baker, 1985; Shanker, Palkar and Nishkala, 1985).

(1984), using tissue cultures, showed that chloroprocaine produced cell membrane fusion, while lignocaine, procaine and metabisulphite did not. Numerous workers have demonstrated other extraneous causes of tissue toxicity, and these are outlined in figure 1. A fuller discussion of the issues may be found elsewhere (Reynolds 1984a, b).

REGIONAL EFFECTS

Regional adverse effects result from the normal action of local anaesthetics in producing nerve conduction blockade, when administered extradurally or intrathecally. The principal effects are hypotension, hypoventilation, Horner's syndrome and hypoglycaemia. All may wrongly be attributed to an idiosyncratic, allergic or toxic effect of the local anaesthetic itself, and the importance of regional blockade be overlooked. Thus motor nerve block is an important contributory cause of hypoventilation, as is preganglionic sympathetic blockade of hypotension. The occurrence of the second two complications is also dependent upon the intrinsic susceptibility of the B (preganglionic, motor) fibres to blockade by local anaesthetics.

Horner's syndrome results from blockade of B fibres in the nerve roots T1–4 (Evans, Gauci and Watkins, 1975). The patient is usually aware of nasal congestion, while ptosis, miosis and dry facial skin are readily observed if unilateral (Clayton, 1983), but some degree of ptosis and miosis may occur very frequently (Carrie and Mohan, 1976), and if bilateral they commonly go unnoticed. Despite the surprising extent of spread implicated in Horner's syndrome, extensive block of other modalities, or even hypotension is not inevitable.

Hypoglycaemia. The suppression by high extradural blockade of the hyperglycaemic response to surgery is well recognized, and depends in part on interruption of afferent stimuli, and in part on blockade of preganglionic sympathetic fibres to the adrenal. Consequently, there is a danger of hypoglycaemia as a result of an exaggerated response to insulin in a diabetic patient given a high extradural block (Romano and Gullo, 1980).

Other regional effects. Urinary retention is an obvious complication of sacral block, but if it outlasts the normal reversible nerve conduction blockade, the cause is unlikely to be regional (implying neurotoxicity), but rather that the bladder has been allowed to become overdistended during the block, or because of urethral trauma in surgery or obstetrics.

Sundry unexpected regional effects are reported following dental (Laskin, 1984) and other regional anaesthesia to the head and neck, but these generally result from transport of local anaesthetic solution to an unintended site, and are therefore considered *focal* effects.

FOCAL EFFECTS

Occasionally, signs of central nervous system toxicity follow abruptly on injection of small doses of local anaesthetic in the head and neck. For example, in stellate ganglion blockade convulsions have been reported following bupivacaine 7.5 mg (Korevaar, Burney and Moore, 1979), aphasia, facial weakness and blindness for 5 min following 2.5 mg (Szeinfeld, Laurencio and Pollares, 1981), and apnoea and coma followed by aphasia and hemiparesis after lignocaine 50 mg (Scott, Ghia and Teeple, 1983). Such localized, profound but brief changes can be accounted for by direct carotid or vertebral artery injection. As the blood flow in any one of these four arteries is about one-quarter of 15% of the cardiac output, Korevaar and his colleagues point out that intra-arterial toxicity would occur when 3.75% of the i.v. toxic dose had been given. Indeed, such a prediction fits the known facts. It therefore follows that a test dose for stellate block should be less than 3.75% of the i.v. maximum safe dose.

Profound lethargy (Barclay, 1981) and even death (Bromage, 1975) have been reported following only 10–32 mg of lignocaine for dental blocks. Subperineural (Bromage, 1975) and retrograde intra-arterial (Aldrete et al., 1977; Aldrete et al., 1978) spread have been evoked to explain these phenomena. Diplopia (Kronman and Kabani, 1984) and temporary blindness (Laskin, 1984) are also reported following maxillary blocks. It has been postulated that injection under pressure may cause local anaesthetic to diffuse through the inferior orbital fissure to the optic nerve, the external ocular muscles or their nerve supply, or again to pass by retrograde arterial spread into the skull.

Interscalene block has been associated with a Jacksonian fit and Todd's paralysis following a bupivacaine test dose to an epileptic patient (Collier and Engelking, 1984) and with respiratory arrest following a massive dose (Lauckner, 1982). A focal element is likely, certainly in the former case.

There have been several reports of respiratory arrest associated with retrobulbar block using lignocaine and bupivacaine in ophthalmic surgery (Hathaway, 1983), on occasion following doses as small as 2 ml of 0.75% bupivacaine (Smith, 1982). The patients were readily resuscitated provided anaesthetic expertise was available. Such phenomena may be explained by subarachnoid spread via the optic nerve or by retrograde spread to the brain via a venous sinus. The respiratory centre is particularly accessible from the ventricles and the frequent citing of bupivacaine probably reflects its popularity and potency rather than any specific danger in its use.

SYSTEMIC EFFECTS

Local anaesthetics entering the systemic circulation produce adverse effects primarily on the central nervous system, but may also produce circulatory effects, methaemoglobinaemia and allergic reactions. Local anaesthetics cannot reach a sufficient systemic concentration to block nerve, ganglionic or neuromuscular transmission.

Central nervous system toxicity

The first sign of systemic toxicity of gradual onset in an unpremedicated patient is drowsiness or inebriation akin to alcoholic intoxication (Reynolds, 1971). People receiving local anaesthesia do not often stand up, but if they do, balance is disturbed (Kjaeregard et al., 1984) as it is by alcohol. Later, circumoral pins and needles, numb tongue, roaring in the ears, visual disturbances, restlessness and twitching may occur, with severe intoxication progressing to convulsions, coma, respiratory and circulatory depression. In toxicity of rapid onset, convulsions may occur immediately, closely followed by circulatory depression, but after a modest i.v. bolus and correct management, these should be short-lived. Major overdose may depress all systems simultaneously, but this does not mean all systems are equally susceptible to the local anaesthetic.

Only cocaine is a true stimulant. Synthetic local anaesthetics do not cause initial CNS stimulation followed by depression, as is reflected in that both lignocaine and procaine infusions have been used for sedation in anaesthesia. Psychotic reactions have, however, been reported during infusions of lignocaine to control arrhythmias (Buckman et al., 1980; Turner, 1982). Shivering during extradural analgesia in obstetrics is sometimes regarded as a systemic effect of bupivacaine, but it may often be observed during labour before extradural insertion, and may be attributable to infusion and extradural injection of cold fluids (Mehta et al., 1984).

CNS toxicity of local anaesthetics depends largely upon their membrane stabilizing effect, thus the i.v. LD_{50} bears a direct relationship to potency in nerve conduction block (fig. 2), a fact which has also been demonstrated in monkeys (Munson et al., 1975). A clear exception to this rule is cocaine, the toxicity of which stems, not from membrane stabilization, but from inhibition of noradrenaline re-uptake. Thus provided equipotent concentrations are used, the danger from accidental i.v injection is similar for all other agents and, of course, much greater for high concentrations of any agent. The differences between them arise if they are given extravascularly for regional blockade, when they are absorbed into the circulation and eliminated from it at rates which are partly independent of potency. These can be predicted to some extent by examining the *subcutaneous* toxicity measured in animals (table I). Clear differences emerge between equipotent agents such as bupivacaine and amethocaine because the latter, a vasodilator (Willatts and Reynolds, 1985), is more rapidly absorbed than the former, while prilocaine is cleared more rapidly from the circulation than the equipotent lignocaine and mepivacaine.

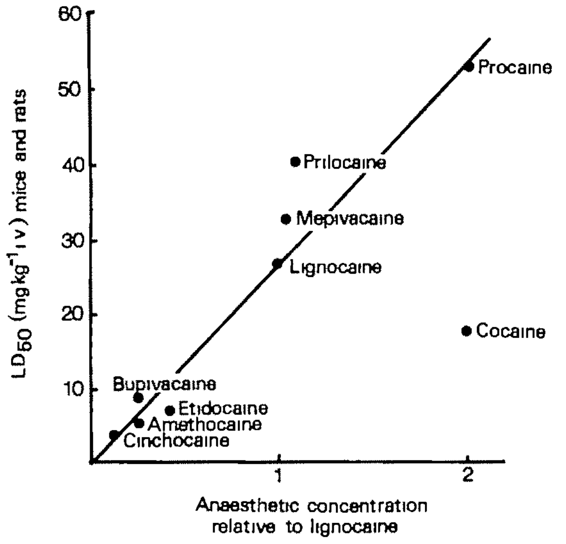

FIG. 2. The relationship between i.v. toxicity and potency. The correlation is good except in the case of cocaine, which has a separate mechanism for producing toxicity.

TABLE I. *Animal toxicity data. (From Reynolds (1970) distilled from various sources)*

	LD_{50}(mg kg^{-1}) (mice)	
	i.v.	s.c.
Amethocaine	8	30
Bupivacaine	8	82
Lignocaine	30	400
Prilocaine	35	900
Mepivacaine	40	270

Circulatory toxicity

Cardiovascular effects of local anaesthetics arise not only from systemic absorption, but also, and much more importantly, as a regional effect of spinal and extradural blockade. The possibility of an allergic response, although unlikely with amides, should also not be overlooked.

Systemically, the CVS is considerably more resistant than the CNS to local anaesthetic toxicity, as has been demonstrated in various experimental animals. Clinically, however, CNS toxicity may be masked by generous premedication with anticonvulsant sedatives such as barbiturates or benzodiazepines, or toxicity may be so overwhelming as to affect both systems simultaneously.

It is well recognized clinically that, in modest doses, lignocaine has therapeutic effects upon the heart, and a useful margin of safety between antiarrhythmic and myocardial depressant doses.

In conscious dogs, cardiac contractility is increased, possibly because of a reflex increase in sympathetic tone (Edouard et al., 1986). Moreover, in low doses, a number of local anaesthetics may increase cardiac output in ventilated dogs (Liu et al., 1982), although procainamide is an exception. In man not only lignocaine but also bupivacaine may increase arterial pressure (Wiklund, 1984), even when three times the maximum safe dose is administered i.v. over 3 h (Hasselstrom et al., 1984).

Adverse cardiac effects are recognized, however, in a number of circumstances. Bradycardia in the fetus, heart block and ventricular tachycardia in the newborn are reported following lignocaine and other agents (Chase and Bray, 1977; van Dorsten and Muller, 1981; Garner, Stirt and Finholt, 1985). Lignocaine infusions in the management of arrhythmia have been associated with bradycardia (Demczuk, 1984), asystole (Antonelli and Block, 1982) and ventricular tachycardia (Burket, Fraker and Temesy-Armos, 1985), while heart block is reported particularly in association with concomitant therapy (*vide infra*: Drug interactions). Ventricular tachycardia (Mallampati, Liu and Knapp, 1984) and fibrillation (Prentiss, 1979) may also follow quickly after convulsions with etidocaine and bupivacaine. Circulatory arrest has, of course, followed gross overdose of lignocaine (Deacock and Simpson, 1964; Buckman et al., 1980), amethocaine (Adriani and Campbell, 1956) and mepivacaine (Sunshine and Fike, 1964) as it has more recently etidocaine and bupivacaine (Albright, 1979; Moore, Crawford and Scurlock, 1980; Moore and Scurlock, 1983). Occasionally, associated factors such as β-blockade (Baraka, Srouji and Haroun, 1983), widespread sympathetic block from spinal, extradural or intercostal administration, or supine hypotension in pregnancy (Marx, 1981; Conklin and Ziadlou-Rad, 1983) combine to precipitate profound hypotension. A fatal outcome has been attributed to "irreversible" cardiac depression from modern long acting local anaesthetics, but it must be stressed that there is *nothing new* in this phenomenon; it was observed with lignocaine before we learnt caution with the older agent. Bupivacaine is known to be three to four times as potent and toxic as lignocaine, yet not infrequently the upper safe dose limit is taken to be similar (table II).

TABLE II. *Toxicity data (mg kg^{-1} or mg litre^{-1}). * The U.K. Data Sheets state that the maximum safe dose of bupivacaine is 2 mg kg^{-1} in any 4-h period. † The maximum safe dose of lignocaine is sometimes said to be 200 mg (Deacock and Simpson, 1964), without any regard to patient weight. (Data from: Reynolds, 1970, 1971; Grimes and Cates, 1976; Zinman, 1976; Moore, Mather and Bridenbaugh, 1977; Yamashiro, 1977; Moore et al., 1978; Moore, Balfour and Fitzgibbons, 1979; Buckman et al., 1980; Moore and Balfour, 1981; Morrell and Bean, 1981; Davison, Parker and Atkinson, 1982)*

	Bupivacaine	Lignocaine
LD_{50} i.v. mice	7.8	30
Maximum safe dose		
Intravenous	0.6–2	2
Other { alone	2*–3.5	3†–4.5
Other { + adrenaline	4–6	7
Toxic plasma concentration		
Mild	1.6–2	3–7
Convulsions	2.3–5	5–10

In nearly every patient convulsions preceded or, when onset was rapid, accompanied circulatory problems, and poor initial resuscitation contributed to the fatality, both in the American patients after extradural and other blocks (Moore, Thompson and Crawford, 1982), and in the British patients after IVRA (Heath, 1982). It must be acknowledged, however, that ventricular fibrillation would appear to be a more frequent feature of bupivacaine than of lignocaine toxicity, although it is undoubtedly precipitated by hypoxia and acidosis resulting from inappropriate or delayed resuscitation. Successful resuscitation has followed some quite massive overdoses of bupivacaine, the records probably being 64 mg kg^{-1} in a dog (Kasten and Martin, 1985) and 11.4 mg kg^{-1} in a man (Davis and de Jong, 1982).

Experimental evidence has been sought to establish the existence of selective cardiotoxicity among local anaesthetics. Much of it is bedevilled with methodological errors, such as the administration of predetermined doses, and of so-called "equivalent" doses of bupivacaine and lignocaine which are nothing of the kind. Moreover, even when a plausible ratio of cardiovascular:CNS toxic doses (CVS:CNS ratio) is demonstrated, this overlooks the actual therapeutic ratio of the agent. Animal work confirms consistently that the CVS is considerably more resistant that the CNS to toxicity from all agents in all species tested (Liu, Feldman and Covino, 1981; Morishima and Covino, 1981; Chadwick, 1982; Liu et al., 1982; Liu et al., 1983), while the ratio would appear to be higher (i.e. safer) for bupivacaine (4:5) than for lignocaine (2:4). However, bupivacaine cardiotoxicity is said to be enhanced more than that of lignocaine by hypoxia and acidosis (Rosen et al., 1985) and by hyperkalaemia (Avery et al., 1981, 1984), although the relevance of the latter factor to clinical practice is disputed (Moore and Bridenbaugh, 1983, 1985).

Although both lignocaine and bupivacaine have been shown to increase the arrhythmogenic threshold to adrenaline in dogs (Chapin et al., 1980), bupivacaine is itself more likely to induce arrhythmias (de Jong, Ronfield and DeRosa, 1982; Marx, 1984; Tanz et al., 1984). The relative effects of local anaesthetics in isolated hearts (Sage et al., 1984; Tanz et al., 1984) are hard to interpret, because predetermined *in vitro* doses are not necessarily comparable to free concentrations present *in vivo*. However, Block and Covino (1981), using the rabbit heart, showed that the depression of conduction and contractility produced by six local anaesthetics was roughly proportional to their potency as local anaesthetics.

It has been suggested that highly lipid soluble agents such as bupivacaine become "fixed" in the heart, a term more relevant to formalin or photography than to pharmacokinetics. As I trust has been explained, irreversible cardiac depression is not unique to bupivacaine or etidocaine.

Adverse vascular effects and hypotension. Concentrations of local anaesthetics that may arise systemically are insufficient to affect blood vessels directly, while the lowest effective concentrations of modern local anaesthetics are constrictor rather than dilator (Aps and Reynolds, 1976; Reynolds, Bryson and Nicholas, 1976). Vasodilatation follows regional blockade of sympathetic nerves or vasomotor centre depression consequent upon severe CNS toxicity. The possible causes of hypotension during local anaesthesia are summarized in table III.

TABLE III. *Causes of hypotension and circulatory collapse during local anaesthesia*

1 Sympathetic blockade from spinal, extradural or intercostal administration.
2 Depression of vasomotor and cardiac centres in the medulla.
3 Hypoxia and acidosis following neglected CNS toxicity.
3 Administration of sedatives/anticonvulsants instead of oxygen.
5 Concomitant treatment with β-blockers etc.
6 Allergic reaction, histamine release.
7 Aortocaval occlusion.
8 Cardiac depression.

Respiratory depression may be associated with systemic toxicity resulting in medullary depression, but is more likely to result from oversedation before regional blockade, or from treating convulsions with diazepam or thiopentone (Moore, Crawford and Scurlock, 1980). It may also be caused by motor block following high spinal or extradural blocks; it may occur as a focal effect following retrobulbar block in ophthalmic surgery (Smith, 1982; Hathaway, 1983) or from possible subarachnoid spread following an excessive dose by interscalene brachial plexus block (Lauckner, 1982). Delayed respiratory arrest has been reported 3 h after uneventful extradural administration, as a quasi side effect of bupivacaine (Holmboe and Kongsrud, 1982), but as the patient was fully conscious but totally paralysed, subdural extra-arachnoid spread, which commonly produces a delayed but extensive effect, is a more likely explanation. An increase in extradural pressure may cause transient respiratory depression (Gissen and Leith, 1985). Respiratory distress (ARDS) occasionally occurs as an allergic response to local anaesthetics (see later).

Causes of Systemic Toxicity

Systemic toxicity affecting principally the CNS and secondarily the CVS, arises because of acute or cumulative overdose. Acute toxicity may be precipitated by rapid entry to the circulation from accidental or deliberate i.v. injection, rapid absorption from a vascular site or transplacental passage. Cumulative toxicity may be aggravated by slow elimination, drug interactions, etc.

The plasma concentrations of local anaesthetics that have been measured in association with mild toxicity and convulsions may vary widely (table II), partly because they may well be changing rapidly following a bolus entry to the circulation. For example, seizures following a dose of bupivacaine 4.8 mg kg^{-1} have been associated with a measured plasma bupivacaine concentration of only 1.1 µg ml^{-1} (Hasselstrom and Mogensen, 1984), while no fits have occurred in association with concentrations as high as 6 µg ml^{-1} (Neill and Watson, 1984), albeit in deeply anaesthetized patients! However, following reasonably steady administration, bupivacaine concentrations of approximately 1.6 µg ml^{-1} (Reynolds, 1971) and lignocaine concentrations of approximately 3 µg ml^{-1} (Aps et al., 1976) are associated with mild toxic symptoms.

Acute toxicity

Acute overdose. Some may believe manufacturers' stated minimum safe doses to be overcautious, others may be ignorant of them, or simple errors may be made. Hardly surprisingly, reactions do occur from time to time, particularly when the maximum safe dose is exceeded (Davis and de Jong, 1982; Lauckner, 1982; Coates, Sanders and Edmonds-Seal, 1983; Goodson and Moore, 1983; Gould and Aldrete, 1983; Moore and Scurlock, 1983).

A fact which is frequently overlooked is that the dose requirement to produce successful block is not directly related to the safe dose. Thus the former dose may depend on frame size, and in the case of peripheral blocks on operator skill, while the toxic dose depends upon body weight.

How often does the tyro weigh his patient, and calculate the maximum safe volume of local anaesthetic, before embarking on some hit-or-miss infiltration procedure?

Those who consider manufacturers' recommendations to be overcautious should appreciate that the maximum safe dose has to be *less* than the *minimum* toxic dose, and while an operator may "get away with it" nine times out of 10, there is no assurance he will be lucky in the 10th, if he is sailing near the wind. Such may even apply with a drug which purports to have a high therapeutic index (fig. 3).

Because the LD_{50} i.v. is proportional to potency (fig. 2), the danger of accidental i.v. injection should be the same for all agents, *provided equipotent concentrations are used.* The risk for extravascular injection however, will also depend upon speed of absorption, and to some extent elimination, of the individual agent. A long acting drug such as bupivacaine is, by definition, more slowly absorbed from the site of action. Thus reference to the data in table II reveals that the margin of safety with bupivacaine if correctly sited should be greater than that of lignocaine; the maximum safe doses sometimes quoted are similar, yet bupivacaine is three to four times as potent. The therapeutic ratio for lignocaine even in single dose by the extradural route would, indeed, appear to be less than that of bupivacaine. Kileff and her associates (1984) found that, even by giving approximately 9 or 10 mg kg^{-1} of lignocaine for Caesarean section, analgesia was inadequate in six of 23 mothers while, not surprisingly, "several" mothers reported symptoms of CNS toxicity. By contrast bupivacaine 1.9 mg kg^{-1} gave a successful block in all patients and no adverse reactions. However, where major overdose or accidental i.v. injection are concerned,

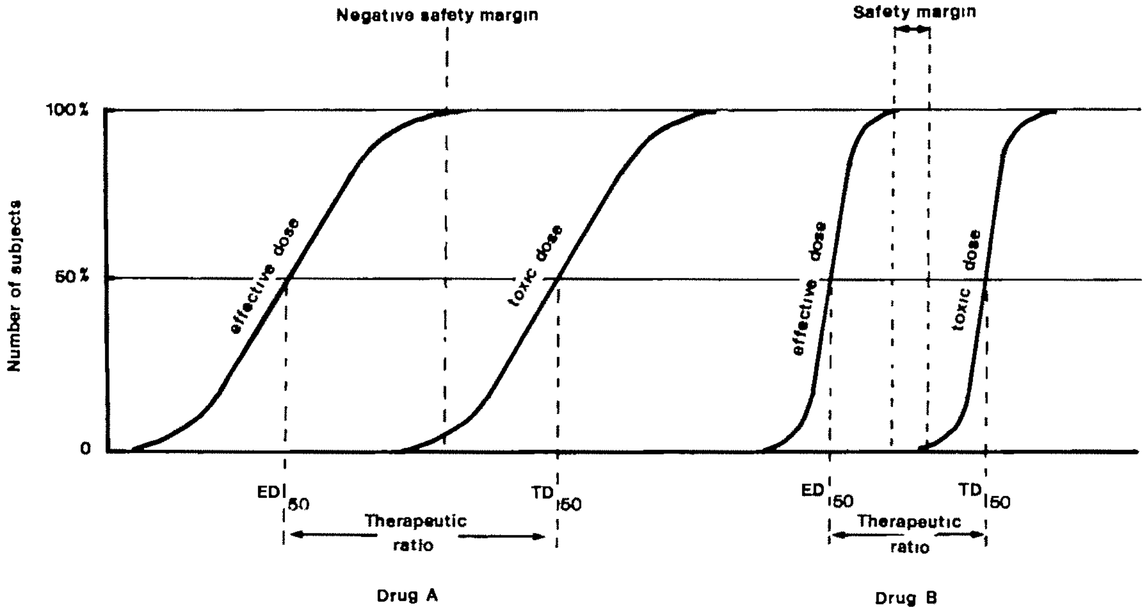

FIG. 3. Theoretical quantal dose–effect curves, used to derive the therapeutic index or ratio ($TD_{50}:ED_{50}$). In practice the actual safety margin (interval between maximum effective dose and minimum toxic dose) does not necessarily bear a direct relationship to the theoretical therapeutic ratio.

the dose of bupivacaine can much more readily approach its lethal dose. Thus bupivacaine as used in recent years may be more like drug A in figure 3: it has a wide therapeutic margin for all normal use, but excessive doses are naturally dangerous. Bupivacaine has become so popular recently among non-anaesthetists partly because, being so potent, it is possible to produce profound effects by overgenerosity with it.

Rapid entry to the circulation. Toxicity may follow small doses injected intravascularly (see also Focal Effects). Accidental i.v. injection should be avoided by keeping the needle moving in peripheral blocks, or by careful aspiration where more appropriate. *Slow* injection is also a vital safeguard. Beeby and Jenkins (1984), in questioning why deaths have occurred from inadvertent i.v. injection during extradurals in the U.S.A. but not in the U.K., suggest that the bacterial filter, used routinely in the U.K., may usefully prevent over-rapid injection. Brief convulsions may occur from "safe" doses of bupivacaine (Morrell and Bean, 1981), while respiratory and cardiac arrest are reported following lignocaine 100 mg injected to a central vein (Grenadier et al., 1981)—a dose that had been found safe in 1100 other patients when injected peripherally.

Local anaesthetics are absorbed very rapidly from mucous membranes, a route by which they are frequently given with scant regard for the maximum safe dose. Toxicity and even death following urethral application of lignocaine, for example, is not new (Deacock and Simpson, 1964) yet, more recently, toxicity has been reported following the administration of 20 mg kg^{-1} by this route (Panacek, Beninger and Albertson, 1984) and of sundry doses of lignocaine and amethocaine via burnt skin and oral mucosa (Barnard, 1984; Wehner and Hamilton, 1984; Parish, Moore and Gotz, 1985).

Intravenous regional anaesthesia (IVRA). Convulsions and circulatory collapse associated with IVRA have been attributed to cuff failure and to drug, yet errors of technique and dosage are probably more crucial, while errors in resuscitation may contribute to a fatal outcome (Reynolds, 1984c). A technique which depends upon perfect occlusion is inherently unsafe because solution may leak past a correctly inflated tourniquet (Rosenberg et al., 1983; Davies, Wilkey and Hall, 1984), convulsions may occur following intended cuff release (Henderson, 1980) and peak concentrations of local anaesthetic may be higher after prolonged than after brief tourniquet time over a range of 10–56 min (fig. 4). Both venous pressure (Lawes et al., 1984) and arterial pressure (Davies et al., 1984) may increase during the procedure to exceed cuff pressure, particularly if prior exsanguination has been omitted. The value of occluding the brachial artery when other methods are impracticable should not be overlooked.

IVRA is contraindicated for leg surgery because an overdose of local anaesthetic is necessary (Hanton and Punchihewa, 1982), while venous occlusion is impossible in the calf, where two bones are present (Davies and Walford, 1986).

Adverse reactions have occurred using lignocaine, prilocaine and bupivacaine (Goold, 1985; Henderson and Sujitkumar, 1986) although fatalities have been reported in the U.K. only with bupivacaine (Heath, 1982). Part of the reason for this is that relatively larger doses of bupivacaine than of lignocaine or prilocaine have been used (Reynolds, 1984c). Although 0.125% and 0.2% bupivacaine have been found to give similar but more prolonged analgesia compared with 0.5% and 0.8% prilocaine (McKeown, Meiklejohn and Scott, 1984), a bupivacaine concentration of 0.2% or even greater has often been deemed necessary, and even found to be safe in experienced hands

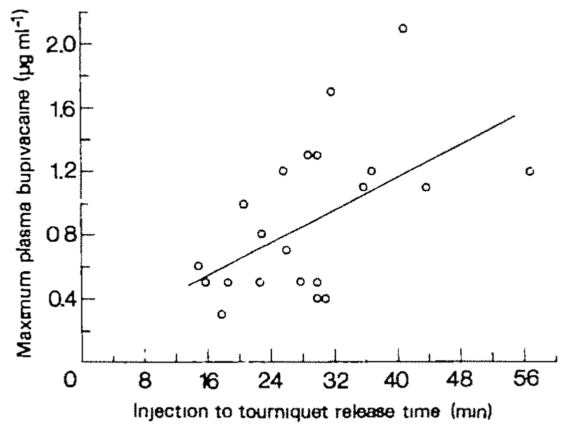

FIG. 4. I.v. regional anaesthesia: relationship between maximum plasma bupivacaine concentration and injection to tourniquet release time. There is a significant positive correlation ($P < 0.05$) indicating the *longer* the tourniquet time the higher the plasma bupivacaine concentration increases (Reproduced from Davies, Wilkey and Hall (1984) by kind permission of the authors and publishers.)

(Magora et al., 1980; Ware, 1982). Apnoea succeeds convulsions abruptly following the rapid entry to the circulation of large doses of any local anaesthetic (Scott, 1984). Neglected hypoxia has undoubtedly contributed to death, but prilocaine, with its more rapid clearance from the circulation, would appear to be the safest choice at present (Tryba et al., 1982).

Cumulative toxicity

Cumulative toxicity may give rise to concern, typically during continuous extradural blockade and during lignocaine infusion in intensive care.

Continuous extradural analgesia. When lignocaine, and in the U.S.A. mepivacaine, were used for this purpose, they had to be given at such a frequency that systemic toxicity was almost inevitable (Reynolds, 1970; Reynolds and Taylor 1970). With the advent of bupivacaine, it became possible to maintain analgesia apparently safely, indefinitely during labour (Duthie, Wyman and Lewis, 1968).

With intermittent or continuous administration of a drug, its plasma concentration can be expected to increase for four to seven half-lives. Thus with a terminal half-life of about 3.5 h (Tucker and Mather, 1975), the concentration of bupivacaine can be expected to increase for 14–24 h, within the timespan of most extradural blocks in labour, while toxicity does not build up further when extradural analgesia is continued for days or weeks (personal observation). The ultimate steady state concentration will depend upon the dose rate, and on the distribution volume of bupivacaine in the given individual. Indeed, Reynolds, Hargrove and Wyman (1973) found that the concentration to which bupivacaine increased in maternal plasma during continuous extradural analgesia was dependent upon total dose, and not at all upon dose rate. From their data they predicted that, using plain bupivacaine, there was a 5% chance of mild intoxication with a dose of 320 mg. This would normally allow bupivacaine top-ups to be given beyond the time to plasma plateau. The finding that maximum bupivacaine concentration is dependent on total dose and not on dose rate has since been confirmed (Laishley, Morgan and Reynolds, in preparation) and is in keeping with pharmacokinetic principles.

With the growing popularity of extradural Caesarean section, the large dose this might necessitate at the end of a long labour raises the possibility of acute-on-chronic toxicity. Thorburn and Moir (1984) reported two such patients. In each case, following difficulty with extending the block and a total dose of 356 and 357 mg respectively, the patient convulsed and went blue, but recovered rapidly on resuscitation. Thompson and her colleagues (1985) confirmed that doses exceeding 2 mg kg^{-1} were associated with some plasma concentrations exceeding that reputed to be toxic (Reynolds, 1971), and that acute-on-chronic extradural blockades produced the highest concentrations, although no signs or symptoms of intoxication were noted.

The U.K. data sheet gives the maximum safe dose of bupivacaine as 2 mg kg^{-1} in any 4-h period. Clearly, in both practical and theoretical terms this limitation is overcautious during the initial period, but should certainly be strictly applied after some hours of topping-up.

Although both etidocaine and prilocaine are cleared more rapidly from the circulation than is bupivacaine, neither is suitable for continuous extradural analgesia because the former gives intense motor blockade at analgesic doses, and the latter increases methaemoglobin concentration.

Lignocaine infusion. Lignocaine, with a terminal half-life of 2.4 h, can be expected to accumulate in the circulation for 12–18 h if given at a steady infusion rate. If given at 2 mg min^{-1} or more for a prolonged period, toxicity will probably occur sooner or later in most individuals, whereas even following a bolus, 1 mg min^{-1} will be ineffective in many cases during the vital early post-infarct period. Using an infusion regimen of bolus followed by 4 mg min^{-1} for 30 min, 2 mg min^{-1} for 2 h, and 1 mg min^{-1} thereafter (the 4–2–1 regime), which was established as a result of i.v. bolus studies in volunteers (Reynolds, 1970), Aps and colleagues (1976) showed that suitable steady state lignocaine concentrations were obtained by 30 min and were maintained. Such a regimen, however, was excessive in the presence of a reduced cardiac output.

Lignocaine is cleared rapidly from the circulation by the liver with a first pass effect of > 0.7, to produce the primary metabolite monoethylglycine xylidine (MEGX) which may contribute to the toxicity. Both agents have been found to accumulate to higher concentrations in the presence of congestive cardiac failure (Halkin et al., 1975; Davison, Parker and Atkinson, 1982), although as lignocaine clearance is flow dependent and liver blood flow is determined principally by cardiac output, it is this latter factor which yields a closer correlation and is associated with an increase in terminal half-life (Aps et al., 1976).

Drug interactions

Drug interactions may also potentiate the toxicity of lignocaine in intensive care, and of bupivacaine.

Hepatic blood flow and therefore lignocaine clearance may be reduced by cimetidine and propranolol (Gilman and Egol, 1983; Ochs, Carstens and Greenblatt, 1980; Feely et al., 1982), while the former may also depress microsomal enzyme activity. Thus lignocaine toxicity during an antiarrhythmic infusion is enhanced by co-administration of these drugs. Ranitidine produces only a small reduction in lignocaine clearance (Robson et al., 1985), and both H_2-antagonists would appear to have a negligible effect on the more slowly cleared bupivacaine.

Interactions may, however, be dynamic as well as kinetic. Cardiovascular collapse is reported following regionally administered bupivacaine in patients treated with verapamil (Collier, 1985) and the β-adrenoreceptor blocker timolol (Baraka, Srouji and Haroun, 1983), although both these drugs were more likely to have been potentiating the effects of regional blockade of sympathetic fibres rather than any systemic effects of bupivacaine.

Prenylamine, the catecholamine-depleting agent used in prophylaxis of angina, contraindicates the use of lignocaine for arrhythmias as this combination may precipitate A–V block (Grenadier et al., 1982) and ventricular tachycardia.

The effect of brain amine concentration on the convulsant threshold to local anaesthetics has been studied in rats. While Ciarlone (1981) found that dopamine and 5-hydroxytryptamine depletion both reduced the convulsant threshold to lignocaine, Niederlehner and colleagues (1982) found that 5-hydroxytryptamine increased the convulsant threshold, but that other monoamines had no significant effect.

Pethidine, which can itself inhibit brain monoamine inactivation, increases the incidence of lignocaine-induced convulsions in mice (Gangarosa, Ciarlone and Hung, 1978), possibly also because norpethidine, its primary metabolite, is actually convulsant. Baraka and Haroun (1985) also found that lignocaine reduced the seizure threshold to fentanyl in man. There is every reason to suppose that narcotics are proconvulsant in man as in animals.

Goodson and Moore (1983) pointed out that the opioid–antiemetic combinations used for sedation in children by many American dentists could reduce the convulsant threshold to local anaesthetics and certainly increased the CNS depressant effects. They report 10 deaths following local anaesthesia for dentistry in children given a combination amounting to more than *three times* the maximum recommended dose of local anaesthetic—usually lignocaine, and opioid analgesic (fig. 5). The problems of resuscitation posed by such gross overdoses in any circumstances are, of course, familiar.

Finally, the place of adrenaline in regional block repays examination. The addition of adrenaline to local anaesthetic solution can reduce peak plasma concentration, particularly following injection in vascular areas, and hence reduces the likelihood of acute toxicity if correctly sited, as witness the low incidence of toxicity following large doses in the Seattle series (Moore et al., 1978). It has been claimed, moreover, that adrenaline might prevent myocardial depression following bupivacaine overdose (Moore and Scurlock, 1983), but the

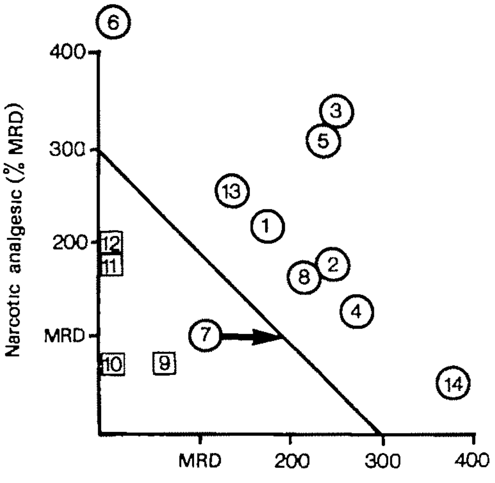

FIG. 5. Relationship between local anaesthetic and narcotic analgesic producing toxic effects. MRD = maximum recommended dose. Squares represent fully reversible reactions. Death or brain damage (circles) occurred when $\%MRD_{LA} + \%MRD_{NA} > 300$. Patient 7 was given lignocaine also for "resuscitation"—indicated by the arrow. Reproduced from Goodson and Moore (1983) by kind permission of the authors and publishers.

patients reported who suffered this complication received considerably more bupivacaine than the ones who did not.

Adrenaline greatly increases the danger should the solution be accidentally injected intravascularly. In some patients reported to be suffering from bupivacaine toxicity, ventricular tachycardia and fibrillation may be attributed to adrenaline (Mallampati, Liu and Knapp, 1984), although these complications are by no means the usual accompaniment of CNS toxicity following regional block (Moore, Thompson and Crawford, 1982). However, another possible explanation for the apparent increase in cardiotoxicity of accidental i.v. bupivacaine in the U.S. may be a greater use of adrenaline-containing solutions, rarely used in the U.K.

Metabolic and other factors

In animals, hypoxia and acidosis have been shown to enhance both the CNS and the CVS toxicity of lignocaine (Englesson and Matousek, 1975; Morishima and Covino, 1981) and the cardiotoxicity of bupivacaine (Rosen et al., 1985). In clinical practice such changes commonly accompany convulsions (Moore, Crawford and Scurlock, 1980) and can be expected to exacerbate cardiac sequelae.

Pregnancy may also increase the circulatory toxicity of bupivacaine in ewes (Morishima et al., 1985), quite irrespective of the contribution by aortocaval occlusion in clinical practice. Crawford (1985), however, reported a series of 27000 bupivacaine extradurals and some 100000 top-ups by midwives, in which there were no deaths or permanent sequelae.

Hyperkalaemia has also been shown experimentally to enhance bupivacaine cardiotoxicity and has been implicated in ventricular tachycardia following suxamethonium (Conklin and Ziadlou-Rad, 1983) and hypotension in a patient with renal failure (Gould and Aldrete, 1983), although in the latter the thiopentone used to treat agitation may have contributed, while hyperkalaemia does not normally occur following suxamethonium given to treat convulsions (Moore and Bridenbaugh, 1985).

Perinatal factors

Local anaesthetics are not noted for producing congenital malformations, although Lee and Nagele (1985) managed to induce neural tube defects in chick embryos following massive doses of lignocaine, procaine and amethocaine.

Decelerations in the fetal heart rate may occur during extradural analgesia using chloroprocaine, lignocaine or bupivacaine (Abboud et al., 1984); these may result from placental drug transfer, or they may be secondary to maternal circulatory changes.

Neonates may break down bupivacaine, mepivacaine and etidocaine more slowly than adults (Reynolds, 1984d) and in experimental circumstances exhibit toxicity at lower total plasma concentrations because of reduced protein binding. Symptoms occur in the same order as in the adult, namely: convulsions, hypotension, respiratory arrest, circulatory collapse (Morishima et al., 1983). In clinical practice neonatal effects have latterly been found to be slight for all agents (Abboud et al., 1982; Kuhnert et al., 1984) and largely limited to hypotonia (Wiener, Hogg and Rosen, 1979), although neonatal depression has in the past been associated with the more cumulative agents lignocaine and mepivacaine (Morishima et al., 1966; Shnider and Way, 1968) rather than with the longer-acting bupivacaine. The maternal and fetal concentrations of the latter increase slowly because it has to be administered less frequently to maintain analgesia (Reynolds and Taylor, 1970). It is sometimes maintained that the low fetal:maternal ratio of bupivacaine, attributable to its reduced fetal binding (Tucker et al., 1970) is of no importance as free concentrations are equal in mother and baby. It is clear, however, that the slow placental transfer of bupivacaine consequent on this reduced binding does retard its accumulation in the fetus (Hamshaw Thomas and Reynolds, 1985), and its extensive use in obstetric extradurals attests to its safety for the baby.

The baby does suffer however, and indeed may die, if he receives excessive doses of any local anaesthetic either following paracervical block (Goodlin, Crocker and Haesslein, 1976), a phenomenon which is not new and probably results from direct entry of drug to the placental circulation (Beazley, Taylor and Reynolds, 1972), or because solution is injected to the head in mistake for the caudal canal (Finster and Popper, 1965) or the paracervical region (Hillman, Hillman and Dodson, 1979).

Prevention and Management of Systemic Toxicity

Toxicity from normal slow absorption of correctly placed local anaesthetic in a dose not exceeding the manufacturer's recommended maximum is not a problem. The danger from accidental i.v. injection is minimized by:

(1) Keeping the needle tip moving in peripheral blocks.

(2) When this is unsuitable, gentle aspiration before injection. This will be reliable down an epidural catheter *only if the tip has multiple holes.*

(3) *Slow* injection of local anaesthetic, which can be halted at the first sign of trouble.

(4) Treating convulsions immediately with oxygen. Provided (3) above is complied with, convulsions will cease before any anticonvulsant could take effect.

(5) Avoiding heavy premedication, which will mask early signs of CNS toxicity, while an anticonvulsant may even suppress seizure activity until circulatory collapse supervenes.

With a more massive overdose than is to be anticipated by obeying the above rules, an anticonvulsant may be required, but should *never* take precedence over oxygen administration (Moore, Crawford and Scurlock, 1980). Although animal work has suggested diazepam might be better than barbiturates in the treatment of local anaesthetic-induced convulsions, thiopentone is quicker to act and produces less hangover (Scott, 1981). However, both agents, but particularly thiopentone, will seriously exacerbate circulatory and respiratory depression.

Persistent convulsions may also be managed using suxamethonium, although it has been argued this might cause hyperkalaemia and so exacerbate cardiotoxicity (Conklin and Ziadlou-Rad, 1983) while not suppressing seizure activity in the brain. Moore and Bonica (1985), however, pointed out that seizures rapidly cause hypoxia, hypercapnia and lactic acidosis, and suxamethonium is to be preferred to thiopentone and diazepam because it stops the muscle activity and hence the lactate overproduction; it permits intubation and artificial ventilation which is essential to treat the acidosis; it does not depress the heart; its half-life is short; it will not cause neonatal depression; and it does not normally increase the plasma potassium concentration.

Early prevention of hypoxia and acidosis should minimize the risk of serious arrhythmias and cardiac arrest but, should they occur following bupivacaine overdose, it must be admitted that patients have survived (in spite of?...because of?) treatment with diazepam, lignocaine (Davis and de Jong, 1982), procainamide, phenytoin (Prentiss, 1979), thiopentone and ketamine (Gould and Aldrete, 1983).

OTHER EFFECTS

Methaemoglobinaemia

Methaemoglobinaemia is repeatedly reported following surface application and ingestion of benzocaine (Douglas and Fairbanks, 1977; O'Donohue, Moss and Angelillo, 1980; McGuigan, 1981; Klein et al., 1983; Seibert and Seibert, 1984; Spielman, Anderson and Terry, 1984), although neither drug nor problem are exactly new. An increased methaemoglobin concentration is also a recognized reaction to prilocaine, the hydrolysis product of which, *o*-toluidine, is the causative agent. A methaemoglobin concentration of approximately 30% is associated with obvious cyanosis and serious signs of cerebral hypoxia, although less than this may cause problems in the presence of cardiorespiratory impairment. A dose of approximately 8 mg kg^{-1} of prilocaine is generally necessary to produce symptoms (Kreutz and Kinni, 1983), but the very young are considerably more susceptible (Ludwig, 1981; Duncan and Kobrinsky, 1983). The onset of trouble is generally some hours after dosage. Haemoglobinopathies, glucose 6-phosphate dehydrogenase deficiency and oxidizing drugs (sulphonamides, antimalarials) may all predispose to methaemoglobinaemia. Treatment involves the slow i.v. administration of methylene blue 2 mg kg^{-1}.

Allergic reactions

Less than 1% of all adverse reactions to local anaesthetics are allergic in origin (Johnson and de Stigter, 1983), yet how often patients tell us they are allergic to lignocaine when they have suffered a faint or an adrenaline reaction in the dental chair. Do they tell dentists the same story when we have given them an overdose or a hypotensive extradural block? Only a small minority of those tested for local anaesthetic allergy show positive responses (Babajews and Ivanyi, 1982; Fisher and Graham, 1984).

Ester local anaesthetics are more allergenic than amides and, moreover, they may show cross-reactivity with *p*-aminobenzoate (a sunscreen as well as a metabolite of procaine), *p*-hydroxybenzoate and its derivative the preservative Methylparaben, which are commonly included in local anaesthetic formulations in multidose vials—rarely used by British anaesthetists. Evidence regarding their contribution to the incidence of apparent local anaesthetic sensitivity is conflicting, however (de Shazo and Nelson, 1979; Babajews and Ivanyi, 1982; Fisher and Graham, 1984), although their allergenic capability is undoubted (Schatz, 1984). Proven allergy to amide local anaesthetics is occasionally encountered, involving prilocaine, mepivacaine, lignocaine and bupivacaine (Brown, Beamish and Wildsmith, 1981; Fisher and Pennington, 1982; Yeoman, 1982), while cross-reactivity within the group is by no means universal (de Shazo and Nelson, 1979; Fisher and Pennington, 1982). The majority of cases involve dental blocks, although lignocaine given by many routes has been implicated in respiratory distress syndrome (Howard, Mohsenifar and Simon, 1982; Promisloff and DuPont, 1983; Woelke and Tucker, 1983; Rooke and Milne, 1984). I have found no record of a verified allergic reaction to extradural bupivacaine.

True hypersensitivity to local anaesthetics may be manifested as general oedema and urticaria, lymphadenopathy, bronchospasm and respiratory distress syndrome. A type I reaction is probably the most usual, although type III may also occur, while contact dermatitis (type IV) is also reported in response to local anaesthetics (Johnson and de Stigter, 1983; Fernandes de Corres and Leanizbarrutia, 1985). Immediate diagnosis can at times be very confusing. Wheezing has been reported during extradural blockade with bupivacaine in labour, leading to the denial of further top-ups, but it also coincided with the advent of a midwife who possessed a dog, the patient having a known allergy to dogs, while bupivacaine sensitivity tests were negative (Mehta and Luxton, 1986). Psychogenic reaction can masquerade very convincingly as allergy. Milam, Giovannitti and Bright (1983) tell of a patient who repeatedly produced psychogenic urticaria following dental blocks. Following a putative allergic reaction, diagnosis is best made by intradermal testing, which carries little danger provided something approaching a 1 in 10000 dilution of the dosage form is used initially, and a 1-mm bleb only is raised.

Management of acute allergic reactions. Adrenaline is frequently stated to be the first line of treatment in anaphylaxis, the logic of treatment

tion not only causes relaxation of bronchial musculature, it also retards further mast cell degranulation while capillary permeability may be reduced (Adriani and Zepernick, 1981). Adrenaline is, of course, contraindicated with volatile anaesthetics (Fisher and Baldo, 1984). Theophylline is a possible alternative, while ketamine, diethyl ether and halothane have been advocated for brochodilatation, although where there is circulatory depression one would hesitate to use halothane. Administration of colloid is also logical, although in severe cases even this may leak from the circulation. Steroids are of course appropriate in such cases, but slow to act. H_1- and H_2-antagonists may be of value, while PEEP may be used to treat pulmonary oedema (Fisher and Baldo, 1984).

SUMMARY AND CONCLUSION

Complications of local anaesthesia in general have been considered in so far as they may be confused with adverse effects of local anaesthetic drugs. Local anaesthetics may give rise to adverse reactions by a number of mechanisms. They affect nerve conduction and vasculature at the site of injection: a *local* effect; but is it unlikely that they ever produce an irreversible noxious effect on nerve fibres. They produce *regional* effects resulting from nerve conduction blockade; hypotension and respiratory depression by this mechanism are frequently mistaken for pharmacological effects of the agent concerned. They produce *focal* effects, usually when carried in high concentration via the arterial supply to the brain. They produce *systemic* effects following absorption or intravenous administration, which are manifested principally in the central nervous system. Ignorance or carelessness are frequently causative factors in serious reactions. Adequate oxygenation is vital in prophylaxis and immediate treatment of systemic toxicity, while resuscitative skill and equipment must always be to hand. Idiosyncrasy or allergy can only rarely be an excuse for adverse reactions to local anaesthesia.

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ENVIRONMENTAL POLLUTION BY INHALATION ANAESTHETICS

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The inevitable, and in the past heavy, pollution of the environment when inhalation anaesthetics are used results in trace concentrations of the agents in question being taken up by the body tissues of exposed personnel. In the case of operating theatre staff it has been demonstrated that these pollutants are present in every medium available for study, ranging from expired gas (Corbett and Ball, 1973) to breast milk (Coté et al., 1976). This paper is concerned with the continuing anxiety as to the extent, if any, to which pollutants cause illness or injury. For reasons that will be presented, the greatest concern has attached to the outcome of pregnancy in women working in the operating room.

As with all studies of toxicity, there are several complementary lines of investigation.

IS THERE A PROVEN MECHANISM?

Over the years there has accumulated evidence of varying quality of the deleterious effect of anaesthetics, notably chloroform, halothane and methoxyflurane on the liver or kidney, or both. These reports refer to concentrations of the agents intended to achieve anaesthesia and not to trace concentrations. Only in the case of methoxyflurane has the mechanism—fluoride production from substantial metabolic breakdown—been clearly shown as a dose-dependent phenomenon in animals and man (Mazze, Trudell and Cousins, 1971). The intense interest of recent years in the role of nitrous oxide as an inactivator of vitamin B_{12}, with consequent interference with DNA production (Nunn and Chanarin, 1985), has strengthened the credibility of some of the main areas of concern about the health of theatre workers, particularly as regards abnormalities of childbearing and disease of the nervous system.

ANIMAL MODELS

Although there is a wealth of reports of histological and gross abnormalities following sacrifice of small animals (mainly rats or mice) which have been acutely or chronically exposed to anaesthetic concentrations of inhalation agents, studies of trace concentrations have focused mainly on reproduction. Several experiments have shown that exposure to subanaesthetic concentrations is associated with a reduction in fetal weight or growth (Pope, Halsey and Landsdown, 1978). This could be a significant observation because such an effect might well be an indicator of fetotoxicity comparable to the effect, for example, of cigarette smoking.

There have been reports of increased fetal resorption (a process perhaps analogous to spontaneous abortion in humans) in rats exposed to nitrous oxide 1000 and 15000 p.p.m. (Corbett et al., 1973) and chloroform 30–300 p.p.m. (Schwertz, Leong and Gehring, 1974), while Coate, Kapp and Lewis (1979) found reduced fetal implantations when rats were exposed to halothane with nitrous oxide. Findings such as these, however, have been the exception rather than the rule. There has been no demonstration of gross fetal abnormality in association with maternal exposure. Indeed, while evidence has been published for regarding inhalation anaesthetics as teratogens (Basford and Fink, 1968; Lane et al., 1980), the effect is neither strong nor consistently reproducible.

Kripke and others (1976) showed that prolonged exposure of male rats to 20% nitrous oxide resulted in abnormalities of spermatogenesis (reduction of the sperm count and multinucleated cells), but this is the only demonstration of an effect that might be mediated through the male.

In all animal studies of toxicity and reproduction, it is important to remember that relative susceptibilities between species are difficult to determine (Cohen, 1980).

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EPIDEMIOLOGICAL STUDIES

In the past 20 years there have been many attempts to collect information about doctors and nurses who work regularly in the operating room, to examine patterns of morbidity as compared with a control group. For the most part it has been assumed, by readers if not necessarily by authors, that any abnormal pattern associated with operating room work should be attributed to exposure to anaesthetics. Without very tight control—and this has proved to be impossible—it is clear that there could be many differences in working style between, say, a woman anaesthetist and a psychiatrist. One example which has been raised without a conclusion being reached is "stress", in relation to which one should consider the extent to which the job might entail periods of acute anxiety in a life-or-death crisis, frustrating boredom or a disturbed sleep pattern.

In the reporting of spontaneous abortion, there are many established factors which influence the incidence apart from occupational considerations: maternal age, history of previous miscarriage, smoking and alcohol habits are examples. Their influence should be controlled in the epidemiological design but, for the most part, that has not been done in studies of operating room exposure.

To achieve an acceptable level of control in observing events which are influenced by many factors or variables, it is obviously necessary to identify cohorts which will yield sufficient numbers for a realistic analysis and to ensure that all appropriate questions can be asked and answered accurately. Even when all the subjects "at risk" can be identified, the number of data may be critically inadequate if the outcome that is being studied is comparatively small. The influential report by Cohen, Bellville and Brown (1971), which suggested more than a three-fold increase in the rate of spontaneous abortion associated with operating room work, was based on data from 117 "exposed" women (doctors and nurses) and 173 controls. The total of miscarriages for all subjects in the study was 33.

Methods of study

Postal questionnaire has been the commonest method, mainly in the form of a *retrospective* enquiry; that is, respondents are asked at a single point in time to give an account of their past medical history. The method is bedevilled by a number of problems. Not everyone replies, and this raises the immediate anxiety that non-responders may have a relevant reason for refusing. For example, a woman who suffers repeated miscarriage might be so distressed by her circumstances that a questionnaire dealing particularly with the subject of miscarriage would be unacceptably distressing for her. Knill-Jones and others (1972) achieved a reply rate just in excess of 80% for women anaesthetists and controls in the United Kingdom, this being the best response in any survey of this type connected with occupation and health of anaesthetists. In a very large study conducted by the American Society of Anesthesiologists (Cohen et al., 1974) reply rates in some groups were less than 50%.

Retrospective studies can be criticized in respect of the accuracy of recall of information. Vessey (1978) has deplored the titles given to some of the enquiries (for example: "Effects of Waste Anaesthetics on Health" (Cohen et al., 1974)), arguing that this might create bias by stimulating those who work in operating rooms to report past events more accurately than those who were replying for control purposes. Certainly, in a study of male doctors in the United Kingdom (Knill-Jones, Newman and Spence, 1975), in which an increase in congenital abnormality of live-born children appeared to be associated with anaesthetic practice, we considered that there may have been bias in reporting because the difference between anaesthetists and controls was almost entirely attributable to the reporting of minor abnormalities. Axelsson and Rylander (1982) found a poorer recall of spontaneous abortion in control subjects compared with operating room staff. The counter-argument is, of course, that in the absence of an explanation for the conduct of the enquiry there might be no replies at all!

There is also the problem that, for any respondent, memory of distant events may be poor. There is some evidence in our own current study in the United Kingdom (see below) that recall of miscarriages which occurred some years previously may be inaccurate, especially in the case of habitual abortion. The design of a questionnaire can have a crucial influence also. Thus, we have found that the provision of checklists in respect of congenital abnormalities of live-born children and of non-obstetric morbidity more than doubles the level of reporting compared with open reporting.

Another deficiency of retrospective studies has been a failure to achieve an effective means of validating the information that has been supplied. Again, in the case of miscarriage it is clearly desirable, in addition to ensuring that there has been no mistake in entering information on the form, to establish the basis for assuming that the respondent was pregnant at all. Was the diagnosis made by another doctor or was it self diagnosis? Was there a pregnancy test? Were the products of conception examined?

There are, therefore, advantages in a *prospective* study in which suitable cohorts can be followed, say annually, by postal questionnaire over a time period that is likely to yield a sufficient amount of data. This has only been attempted once, by the author and Dr R. P. Knill-Jones, in a study commenced in 1977 and due to end in late 1986. The work, supported by the United Kingdom Medical Research Council and endorsed by the Departments of Health, involves annual mailing of all women doctors aged 40 years or less at the time of recruitment to the enquiry and who work in the U.K. National Health Service hospitals, irrespective of specialty. The response rate has been consistently in excess of 80% for new entrants and there is less than 2% loss to the study of women who have replied in earlier years. We believe that the main reason for non-response is a difficulty of effective mailing. Women in this young age range are highly mobile, both within the U.K. and abroad. There is the additional uncertainty of compliance by those who leave medical practice for domestic reasons. We have found hospital addresses to be unreliable for contact and prefer home addresses which are taken from the Medical Register but this, too, may not be totally successful if the surname is changed following marriage. Thus, we consider the response rate would be difficult to improve upon and that our cohort is well motivated to assist in the enquiry.

Some 11000 women have been recruited to the U.K. prospective study and there are details on approximately 7300 pregnancies. The questionnaire has a section on non-obstetric morbidity in which the respondents complete a check list for the common conditions, with open reporting of rare disease. In recent years the list has been altered slightly to take account of the possibility of neuropathy resulting from nitrous oxide exposure; so far, no alarming pattern has emerged. Information includes a statement on whether or not the woman was absent from work as a result of a particular illness, as a measure of its likely severity. Vessey (1978) has pointed out that retrospective studies may miss important instances of disease which is so severe as to necessitate giving up work, thus removing the person from the occupational group under scrutiny. These objections apply very obviously to the assessment of the incidence of cancer. While a prospective study may not be free of this limitation, it has been possible in the present enquiry to note the onset of conditions such as cancer and to monitor deaths if they occur. Subject to the caveat that the study is not complete, it should be noted that no obvious association between operating room work and cancer has been found.

The major part of the questionnaire is devoted to obstetric history, with a section for pregnancies resulting in live-born children and another for miscarriage. Information available for control of these observations includes: a measure of the extent (hours per week) to which the woman (and her partner) have been exposed to the operating room environment, use of anaesthetic gas scavenging systems, smoking and alcohol habit, exposure to ionizing radiation, previous diseases such as rubella and the time of ceasing medical practice before delivery. There is also detailed information on contraception, because previous practices may have an influence on child-bearing and also because it allows close examination of reports of infertility.

The expected statistically significant relationship between maternal age, smoking, previous pregnancy outcome, alcohol consumption and the frequency of spontaneous abortion has been evident in the study for some years. At the moment there is no obvious relationship between hours worked or specialty and miscarriage. The previously known relationship between smoking and birth weight has emerged. There is also a relationship between hours worked in the operating room and birth weight, although this may disappear after adjustment for other factors including the racial origin of the respondents. At present the mean birth weight of children born to women working as anaesthetists or surgeons is significantly less than that for children born to other women working in hospital posts, even after adjustment for known factors.

The definitive analysis of the U.K. prospective study is expected to be ready for reporting at the end of 1986.

Datalinkage or registry studies result from the availability of relevant information in a central register. In Sweden, for example, a Medical Birth Registry was initiated in 1973. It holds information on pre-natal care, delivery and post-natal examination of newborn infants for more than 99% of all pregnancies in the country. There is also a reliable registry of Swedish nurses and a less complete register of spontaneous abortions (involving stay in hospital) and of legally induced abortions; the abortion register covers 70% of counties in Sweden. All these registers have as an identifier, a unique number given to each Swedish citizen at birth. It is possible to link data from the registers to examine various hypotheses, and Ericson and Källén (1979) examined the outcome of 494 pregnancies in Swedish women who, in 1973 or 1975, had worked in the operating room for at least one-half of the gestation period, with controls. Exposure to anaesthetic gases was assumed, not verified. This type of enquiry offers the benefit of a complete data set as compared with the uncertainty of non-responders in a postal questionnaire. It also obviates bias in reporting and inaccuracy of recall information.

There was no obvious influence of operating room work on the rates for spontaneous abortion, perinatal mortality or congenital malformation and the birth weight distributions for "exposed" and control pregnancies were similar. There was a possibility, however, that the incidence of short gestation periods (less than 37 weeks) was greater in exposed women.

The same authors published a similar study covering the period 1973–78 and restricted to nurses (Ericson and Källén, 1985). Again, there was no apparent influence of exposure on the rates of spontaneous abortion, congenital abnormality, still birth or death of the baby within the first seven days of life. Fifty-eight babies born to exposed mothers weighed less than 2.5 kg at birth (4.4%), compared with 46 (3.3%) in a control group of nurses working in medical wards. The difference is not statistically significant and the observation may be confounded by the fact that the rate of twin births (1.2%) to exposed women was approximately twice that of the controls. The authors' previous finding relating to the gestation period was not confirmed.

Because exposed Swedish nurses may be either operating room nurses or nurse anaesthetists, Drs Ericson and Källén included within the study reported above a case–control study. In case–control studies individuals who are diseased (cases) are compared with a non-disease group (controls) to examine the occurrence of relevant factors in the past. In this instance, details of working practice in the operating room and the likely level of exposure to anaesthetic gases were sought by postal questionnaire from 25 nurses whose infants had died or had serious congenital malformations (cases) and 50 nurses with normal infants. Replies were received from 74 of the 75 and all were "exposed" nurses within the frame of the main study. No discernible difference in working pattern was found between cases and controls.

Hemminki, Kyyrönen and Lindbohm (1985), from Finland, have reported a registry-based study of nurses in which they examined the influence of a variety of occupational risks on abortion and congenital malformation rates (including anaesthetic gas exposure and the handling of cytotoxic agents) in the period 1973–80. Whereas handling of cytotoxics was associated with a 130% increase in abortion rate (230% where there was no history of previous fetal loss), in a case–control study (Selevan et al., 1985) no significant influence of anaesthetic gas exposure emerged.

Thus, excluding the U.K. prospective study on the grounds that it is incomplete, data linkage studies have yielded no significant concern about operating room work and reproductive mishap and the anxieties of the past 15 years or so have been based largely on retrospective questionnaires.

Table I lists the retrospective enquiries that have received the greatest attention, indicating in a very general way the main findings in relation to women respondents only. The table takes no account of the marked differences in the quality of these studies (bad design or poor reply rates), nor does it reflect the degree of objectivity that was brought to bear on the conclusions reached in each case. The reader is referred to the original publications for detailed information and to the helpful book by Dr E. N. Cohen (1980) which offers a critical review of studies published up to that year.

Enough has been noted above to indicate that the mere fact of agreement between studies that are or may be flawed does not necessarily prove that an occupational health problem exists. For this reason it is valuable to have an independent overview of these epidemiological studies.

Tannenbaum and Goldberg (1985) considered

TABLE I. *Studies using retrospective questioning of reproductive outcome in female doctors or nurses known to be working in the operating room or designated as a working anaesthetist in the course of a pregnancy. + = Higher incidence of disorder compared with controls; in some instances, in the absence of an appropriate control group, an incidence assumed by comparison with the population at large to be abnormally great. – = Negative finding. * Reviewed by Tannenbaum and Goldberg (1985). † Considered and ‡ analysed by Epistat group (Buring et al., 1985)*

	Spontaneous abortion	Congenital abnormality	Country
Vaisman (1967)	+	–	U.S.S.R.
Askrog and Harvald (1970)	+		Denmark†
Cohen, Belville and Brown (1971)	+		U.S.A. (California)†‡
Knill-Jones et al. (1972)	+	+	U.K *†‡
Rosenberg and Kirves (1973)	+		Finland*†‡
Corbett, Cornell and Endres (1974)		+	U.S.A. (Michigan)*†
Cohen et al. (1974)	+	+	U.S.A.*†‡
Knill-Jones, Newman and Spence (1975)	+	+	U.K.*†‡
Pharaoh, Alberman and Doyle (1977)	–	+	U.K.*†
Mirakhur and Badve (1975)	+		India
Rosenberg and Vanttinen (1978)	–		Finland*
Tomlin (1978)	+	+	U.K.*
Cohen et al. (1980)	+		U.S.A.*†
Axelsson and Rylander (1982)	+		Sweden*†‡

14 reports relating to anaesthetic exposure and reproductive outcome. Eleven are indexed in table I. The three others were the data linkage study of Ericson and Källén (1979), an American study of male oral surgeons and dentists (Cohen et al., 1975) and a Belgian study of anaesthetists and nurses (Lauwerys, Siddons and Misson, 1981). Tannenbaum and Goldberg concluded that they could not accept that any adverse effect of anaesthetic gases on reproductive outcome could be accepted on the basis of their review of the retrospective enquiries:

> "...after examination of methodology...the validity of the results can be seriously questioned. The consistency of the results may be explained in part by consistency of the methodologic problems, specifically lack of criteria for exposure or outcome, poor survey response rates, selection bias, lack of validation or outcome, recall bias and lack of control of potentially confounding variables."

These authors called for a prospective cohort study or, ideally, the development of morbidity and mortality registers similar to those created in Sweden.

The American Society of Anesthesiologists commissioned a group of epidemiologists and biostatisticians (Epistat Associates) to examine the same information. They reported in 1982 and an abridged version of the report was published by Buring and others (1985). Sixteen reports were studied. Four (Bruce et al., 1968, 1974: Doll and Peto, 1976, 1977) related to mortality studies "which showed no relationship with prior occupational exposure". Ten are indexed in table I and the reports of Ericson and Källén (1979) and Cohen and others (1975) were considered also. Of these, seven were then excluded on account of non-comparable control groups or data that could not be interpreted fully, or because the publications related to outcome among wives of exposed men or a study of dentists (who were held to have a pattern of anaesthetic exposure substantially different from that of operating room staff). This left five studies indexed in table I.

The *relative risk* (RR) was taken as a measure of

TABLE II. *Relative risk (RR) for spontaneous abortion and congenital abnormality of live-born children with 95% confidence limits in parentheses. Exposed* v. *non-exposed women. See text for further explanation.* (*From Buring and others (1985)*)

	Spontaneous abortion	Congenital abnormality
Physicians	1.4 (1.2–1.6)	1.4 (1.0–2.0)
Nurses	1.3 (1.1–1.4)	1.1 (0.9–1.4)
All subjects	1.3 (1.2–1.4)	1.2 (1.0–1.4)

the strength of association between operating room exposure and disease. RR is simply a ratio of disease rates in exposed *v.* non-exposed subjects. An estimate of true RR is given by the 95% confidence limits: when the range of the confidence limits does not include 1.0, RR is statistically significant with $P < 0.05$.

Table II shows the RR values from the combined analysis of the five studies. It can be seen that, for both female doctors and nurses, a statistically significant risk emerged in respect of exposure and spontaneous abortion, although in both groups the estimated increased risk is comparatively modest. RR for congenital abnormality exposure is smaller and, in such a complex sphere of investigation, it would be potentially misleading to assume that such values are a basis for concern.

CONCLUSIONS

Fifteen years after the initial widespread concern about operating theatre pollution and health, the conclusions are obviously becoming much less alarming. This paper has concentrated on the pitfalls in epidemiological design which may have led to spurious findings in the past. Certainly, it is true to say that the more precisely designed studies have yielded the most reassuring results. On the other hand, in the same period there have been significant changes in patterns of drug use and techniques—a tendency by some anaesthetists to minimize the use of inhalation anaesthetics, especially the volatile agents, and the introduction of scavenging. In the United Kingdom, at least, it is likely that, on average, the anaesthetist spends fewer hours in the operating room than did his or her predecessor.

The cynic might ask if we have not simply endured the creation of a false hypothesis with consequent inappropriate diversion of time and resources to enquiries that might best have been left alone. That argument is erroneous. It should be remembered that in the early 1970s there was great difficulty in recruiting to the practice of anaesthesia sufficient numbers of doctors to sustain surgical services, and many of those who took part were women, often working on a part-time basis. If the *prima facie* grounds for concern had not been investigated further and these doctors had chosen to leave anaesthesia in the interests of their health, perhaps joined by a significant proportion of operating room female nursing staff, surgical services would have been drastically impaired. Thus, attempts at monitoring the patterns of health in operating room workers were and are fully justified. It should be realized, also, that the possibility of some small influence on childbearing associated with operating room work still cannot be positively excluded. A demonstration of an influence on birth weight, for example, would merit serious consideration and perhaps indicate the need for further monitoring.

It will be clear that, even with the best design, epidemiological methods are a relatively blunt instrument for the investigation of obstetric mishap, especially when the numbers available for study are small. In the United Kingdom, in the 1970s, consideration was given to the possibility of studies in which products of conception could be analysed in the laboratory, but the emotional and, later, legal constraints rendered that virtually impracticable.

There is no doubt that effective access to health records such as is possible in Sweden greatly facilitates occupational health surveys. The growth of occupational medicine as a discipline in the development of occupational health services within the United Kingdom National Health Service may lead to international collaboration in data-linkage studies.

Notwithstanding the relatively reassuring conclusions that can be drawn about the operating room as a working environment, two points should be emphasized. Such abnormal patterns as may have occurred in the past or may emerge in the future cannot with certainty be attributed to exposure to trace concentrations of anaesthetics in the atmosphere. Classically, the demonstration of toxicity requires a known mechanism, specific lesions or injuries and a clear indication that the incidence of these ceases or abates following withdrawal of the suspected toxic substance. None of these criteria has ever been adequately fulfilled for the inhalation anaesthetics as environmental contaminants. We should not be blind to the possibility that other environmental factors existing or still to be introduced could pose a threat to health; the recent concern about the handling of cytotoxic agents is a good example.

Epidemiological methods will never offer total reassurance that in some circumstances, however extreme, an adverse effect on health cannot be produced by the working environment. Thus, it could be that very high levels of exposure to anaesthetics or other influences are indeed harmful. All that can be said is that, on the basis of the study of populations of anaesthetists and other operating room workers within individual countries, no clear evidence exists.

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INVESTIGATION OF ALLERGIC AND HYPERSENSITIVITY REACTIONS TO ANAESTHETIC AGENTS

J. WATKINS

Some three million general anaesthetics are administered annually in the United Kingdom, for a variety of surgical procedures. It is inevitable that untoward reactions will occur, but it is the incidence of the reactions which gives cause for concern.

Lunn and Mushin (1982) described almost 300 deaths per year totally attributable to anaesthesia and a much larger number, 1800 deaths, in which anaesthesia may have played some part. Contrary to general opinion, these deaths were not restricted to "high risk" surgical patients and the authors made the unpalatable observation that the majority of the deaths are probably avoidable. Clearly, the deaths represent predominantly mistakes or errors of judgement, rather than idiosyncrasy or hypersensitivity, although our laboratory suggests that up to 100 of the 300 directly associated deaths may result from the latter mechanisms (Watkins, 1985a).

A more common problem is that of anaesthetic morbidity, with perhaps 10000 patients per year involved in a variety of clinically significant adverse reactions, usually manifest immediately after the induction of anaesthesia and with the general characteristics of immune hypersensitivity reactions. These reactions are in fact characteristic of the i.v. administration of any substance, not simply of anaesthetic drugs, and similar reactions are encountered to plasma substitutes and to the growing use of radiocontrast substances. The reactions may range from relatively minor systemic effects, notably flushing and minor degrees of hypotension (which may not even interrupt the surgical procedure), to varying degrees of brain damage following cardiac arrest. All these patients pose problems for the future and an enormous drain on resources, in time spent in intensive care and repeat surgical procedures.

Limitations of clinical observation alone

The clinical manifestations of these hypersensitivity-like, *anaphylactoid*, reactions do not reflect the mechanism of the reaction, be it immune (specific to the drug administered) or non-immune (just as likely to occur with entirely different drugs). Indeed, in clinical trials it has proved possible to duplicate the clinical manifestation of minor anaphylactoid reactions simply by the administration of minute amounts of exogenous histamine (Lorenz et al., 1982). While the management of clinically severe anaphylactoid reactions is essentially identical, whatever the cause, future management of the patient, including prophylactic measures, is dependent on a full understanding of the mechanism of the reaction. In a wider context, such investigations should increase our knowledge of the patient likely to be at anaesthetic risk and lead to the synthesis of safer drugs by the pharmaceutical industry.

PRACTICAL METHODS OF INVESTIGATING REACTIONS

Once the anaesthetist has stabilized the patient, thought should be given to investigating the cause of the reaction. If the surgical procedure has been abandoned, a repeat procedure may be required at some early date, posing immediate problems to the anaesthetist in terms of choice of drugs or of techniques. Even in the absence of such urgency, the patient is certainly likely to require further general anaesthetic procedures, throughout life.

No *single in vivo* or *in vitro* test will provide the answers: a correct assessment of anaphylactoid reactions requires close co-operation between the anaesthetist involved, the patient, and an experienced clinical immunologist. The aim should be

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to identify the causative drug and the mechanism involved. The latter is probably the most important for the patient's future care. For example, the characteristics of *immune* response forecast an *enhancement* of reaction intensity on further exposure. If in doubt of the causative drug in an established or probable immune situation, the anaesthetist should abandon *all* drugs used in the previous reactive situation. In practice, a little detective work with the sequence of drug addition and the onset of untoward clinical signs will usually restrict this to elimination only of the drugs used to induce anaesthesia and not those used for premedication. With a *non-immune* response, substitution of the incriminated drugs with new ones may still generate hazardous situations. In general terms, in the non-immune situation it may be better to contemplate anaesthetic regimens alternative to the i.v. induction route—inhalation induction or regional blockade.

Mechanisms

The principal causes of immediate anaphylactoid shock associated with anaesthesia and surgery are tabulated in table I. While anaphylactoid and anaphylactic mechanisms are equally likely to generate life threatening responses, there is a general feeling that antibody-mediated anaphylaxis is less likely to be reversed, even by prompt treatment of the patient. Diagnosis of anaphylaxis must remain a subjective assessment since, by their very nature, anaphylactoid reactions do not lend themselves to anything but retrospective clinical investigation.

Not all of the mechanisms listed in table I occur with the same frequency and, equally, mechanisms are not mutually exclusive of each other. The majority of reactions, whether ultimately fatal or non-fatal, are likely to represent errors of judgement on the part of the anaesthetist and the surgeon (table I) (*cf.* Lunn and Mushin, 1982). Genuine *drug involved* reactions are confined to mechanisms (1) and (2) of the anaphylactic and anaphylactoid mechanisms, respectively (table I). Although true *drug specific* reactions are confined to anaphylactic, antibody-mediated mechanisms, nevertheless both (1) and (2) of the anaphylactoid mechanisms may still reflect broad *class specific* features of groups of drugs and other compounds, such as the characteristic molecular groupings common to neuromuscular blocking agents (Assem, 1984) and the chemotoxicity of all radiocontrast materials, reflecting their general properties of hyperosmolarity and hydrophobicity (Bielory and Kaliner, 1985).

TABLE I. *Classification of mechanisms*

Anaphylactoid shock—arises from:	
Anaphylactic mechanisms	Anaphylactoid mechanisms
(1) Type 1 immunological hypersensitivity (antibodies bound to cells; cytotropic anaphylaxis)	(1) *Direct* action of drugs on cells rich in vasoactive substances
(2) Anaphylaxis mediated by circulating antibodies (aggregate, *immune complex* anaphylaxis)	(2) *Indirect* release of vasoactive substances through activation of intermediary biological systems
	(3) Drug interactions, and drug overload
	(4) Aggregate (*non-immune*) anaphylaxis. A further complication of (3) and plasma substitutes
	(5) Unforeseen patient pathology
	(6) Surgical stimulation
	(7) Psychosomatic response

Nancy Recommendations

Guidance on the systematic investigation of anaphylactoid reactions was given at a one-day workshop held in Nancy in March 1982, which brought together anaesthetists and clinical immunologists from Europe to decide upon a standard assessment procedure (Laxenaire, Moneret-Vautrin and Watkins, 1983). Several of the important communications at this meeting were published later in the French literature (*Annales Françaises*, 1982). It will be helpful to review the original procedure briefly and then draw particular attention to those points which should always be observed, their modifications, and limitations of interpretation. For convenience, the recommendations of the joint anaesthetic and immuno-allergological workshop may be considered under three broad headings: (1) Assessment during the anaphylactoid response; (2) assessment 6 weeks later; and (3) communication of the conclusions drawn from (1) and (2).

Assessment during the anaphylactoid response

The immediate assessment is concerned primarily with establishing the reaction mechanism. It was recommended that blood samples should be taken into tubes containing ethylenediamine tetracetic acid (EDTA) and into heparin tubes for haematology, immunology, and histamine assay. The first sample should be taken as soon as possible after commencement of the adverse reaction and further samples should then be taken 1, 6, 24 and 72 h after the incident. Routine haematology, including haematocrit, is necessary to ensure correction of plasma protein concentrations for fluid changes brought about both by the reaction itself and from exogenous fluids administered in the management of the reaction. The full differential white cell counts supplied "routinely" from the sophisticated analysers used by modern haematology departments have high precision. This means that even minor shifts in platelet and white cell numbers have high statistical significance, particularly the disappearance of basophils in initial reaction samples, which is highly indicative of a Type I immune response (Theobald-Segalen et al., 1982).

The humoral assessment can include measurement of IgE concentrations, histamine (lithium heparin plasma), and complement concentrations and function.

IgE concentrations are readily measured by radioimmunoassay using the PRIST kits sold by Pharmacia (U.K).

Histamine. The requirements associated with blood sampling for histamine (Lorenz et al., 1981) effectively preclude this assay from serious reactions. This is particularly unfortunate, since its proven involvement would make H_1- and H_2-antagonism mandatory in the future use for that particular patient.

Complement assessment includes the measurement of C3 and C4 and the assessment of the degree of conversion of these proteins. This is achieved by simple immunochemical techniques. In simple terms, involvement of C3 *and* C4 is likely to implicate an immune reaction, C3 alone a non-immune reaction. The latter implies a broad reactivity to a *class* of substances, for example radiocontrast substance, or to drugs using Cremophor in their formulation, rather than to a *specific* drug structure.

Assessment 6 weeks later

This is made to diagnose the causative drug(s). The patient is referred to an experienced clinical immunologist. The anaesthetist provides comprehensive details of the adverse incident, a list of *all* drugs administered and their sequence, a list of previous anaesthetics and the drugs administered (and any untoward sequelae) and any other medical history which may be relevant, including personal or familial traits of allergy or asthma and details of any recent illnesses. The IgE concentrations obtained from the immediate assessment will substantiate any clinical evidence of atopy, particularly if the testing laboratory has screened for specific IgE antibodies to the most common airborne allergens, house dust mite and grass pollens.

All the above are risk factors inherent to the patient at the time of anaphylactoid response. On the basis of this evaluation, and if the findings of the *immediate* assessment indicate an immune mechanism, *then* specific antibody response (anaphylaxis) to one or more of the administered anaesthetic drugs may be sought. Three tests were recommended, involving both *in vivo* and *in vitro* aspects of immunity:

(a) Skin tests at low dilutions of the drugs (1 in 1000; 1 in 10000).

(b) Human basophil degranulation test (Benveniste technique).

(c) Antibody passive transfer tests (Prausnitz–Kusner (PK) tests).

Two positive of these three tests would be considered to be a positive identification.

Communication of the conclusions

Results from these tests are then made known to:

(a) The anaesthetist, together with recommendations for future management. If a specific drug response has been identified, then that drug must never be re-administered to the patient and this fact must be entered on his/her hospital records.

(b) The patient. The final procedure recommends that the patient should be given an anaesthetic card with the names of the hazardous drugs entered and that he should carry this at all times.

Limitations in an ideal procedure

The Nancy procedure must represent an ideal, and it would appear to be infrequently achieved, even by our enlightened colleagues in Europe. It can be actually improved by "early" blood sampling during the first 30 min following onset of the reaction, although usually the anaesthetist is far too busy stabilizing his patient to worry overmuch about future anaesthesia! The time sequence indicated was a compromise for the delegates present: the Sheffield Unit prefers immediate (i.e. as soon as possible), 1, 3, 6, 12 and 24 h. Unfortunately, the 72-h sample frequently reflects increases in the acute phase proteins as a result of the body's stress response to the reaction trauma. A better baseline is achieved several weeks later, even at the 6-week assessment point.

In Sheffield, in order to prevent error by blood samples being inadvertently taken into containers containing the wrong stabilizing agent, we now request only EDTA blood samples, since these are compatible with the requirements for both haematology and serology. Duplicate blood samples should be taken as soon after the procedure (immediate, 1, 3, 6, 12 and 24 h) as convenient to staff and ward schedules.

The use of EDTA confers long term stability of frozen plasma samples over those taken in citrate or heparin, presumably because of the highly effective immobilization of Ca^{2+} ions. It is necessary to use plasma rather than serum to assess both concentrations and function of complement components which are compromised by blood clotting mechanisms. The involvement of both C3 and C4 is highly indicative of an immune reaction which does not involve IgE antibodies. Complement C3 conversion *alone* (alternative pathway activation) is an indication of a specific non-immune mechanism. The incidence of the latter has declined rapidly with the disappearance of Althesin from the anaesthetic scene, although it is still encountered with radiocontrast media as a predominant mechanism, and sometimes with dextran. Possible angio-oedema traits may be catered for by the assessment of C1 inhibitor concentration in plasma and its *function* measured in serum. The latter may be made on serum separated from freshly clotted blood taken at any convenient time, after the patient's recovery.

The complexity of the plasma complement system makes it prone to activation at several points, including inhibition of the normal system "inactivator" enzymes and in response to aggregates of infused molecules resembling immune complexes (for example certain dextrans and albumin preparations).

Involvement of plasma proteins, and particularly complement components, is seen as a reduction, and subsequent recovery, pattern (fig. 1). This reflects their *immediate* involvement in the reaction mechanism, followed by a very slow replacement, after several hours, from both the extravascular fluid pool and fresh protein synthesis. It is this *projection* of the reaction, not the reaction itself, which we can follow readily. Proteins may be directly consumed in the reaction, but more often simply "converted" from native molecules into inactive species as a result of the release of their biologically active polypeptide moieties. Until this inactive denatured protein is catabolized, plasma protein *concentrations* remain almost constant, since the usual immunochemical quantitation techniques make no distinction between native and inactivated protein. Other techniques to demonstrate such changes are necessary and various types of simple immunoelectrophoretic procedures have been described, particularly in relationship to complement components (Watkins, 1982). The term conversion (native to inactive form) is widely used synonymously with native C3 activation by both immune (classic pathway) and non-immune (alternative pathway) mechanisms. However, the other native complement components show conversion, as do

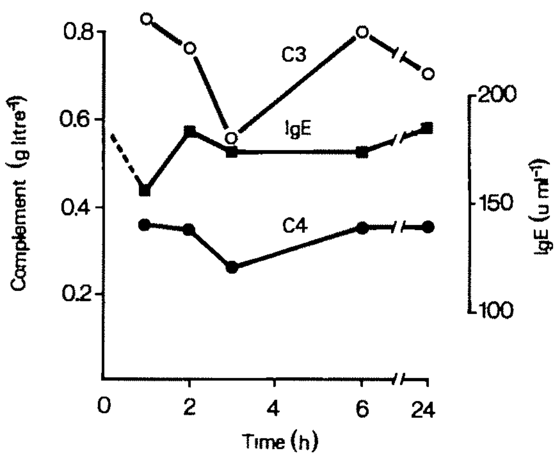

FIG. 1. Plasma profile of a severe anaphylactic reaction in an elderly man following induction of anaesthesia with thiopentone and alcuronium. The patient suffered cardiac arrest which, although reversed, resulted in extensive brain damage and death several days later. The reaction appears to have incurred immune mechanisms of both the cytotropic (IgE) and aggregate anaphylaxis type, the latter involving the classical complement cascade, with C3 and C4 involved. Note the "immediate" slight but significant decrease in IgE. There is a much delayed (3-h) decrease in C3 and C4, representing a projection of the initial involvement of native proteins in the reaction and the subsequent slow removal of these now denatured enzymes. Parallel measurements showed that the plasma immunoglobulin concentrations (IgG, IgA, IgM) were constant at the various sample times, implying that the complement changes were not caused by changes in plasma volume.

proteins of analogous biological systems such as fibrinogen and plasminogen. The consequences of clinical intervention on the complement system have been reviewed (Watkins, 1985b).

Immunoglobulin IgE frequently shows a reduction and recovery pattern similar to that of complement proteins when involved in reactions (fig. 1). This is particularly evident with increased plasma concentrations (> 100 u. ml^{-1}). This behaviour of IgE response to *i.v.* therapy is bizarre. The change is too great to indicate specific antibody and again must represent rather drastic equilibration between cell-bound IgE and the circulating material in the vascular and extravascular pools. On the basis of other studies, the author is of the opinion that this pattern of IgE response is consistent with a genuine Type I allergic reaction; he accepts that the view is controversial! Immunoglobulin IgE concentrations around 1000 u. ml^{-1} and greater are consistent with atopic states and an indication, perhaps, of a patient at risk to multiple i.v. exposure to the same drugs. Assay kits (RAST) to specific anaesthetic drugs are not yet commercially available, although some interest is being expressed by Pharmacia and a working system to a few of the more common drugs is being established (Sheffield–Pharmacia studies).

In contrast to the high-IgE atopy trait, which involves some 10% of the population, interest is gathering in patients with *low* IgE concentrations (< 15 u. ml^{-1}) in their plasma. Some 10–20% of the population exhibit such low concentrations. When presenting as surgical patients, these individuals appear both to be prone to non-immune mediated clinical reactions and to produce positive intradermal skin tests with drugs known to have high histamine release potential, particularly neuromuscular drugs (Lavery, Clarke and Watkins, 1985). One hypothesis is that these unfortunate patients respond to drugs administered by the i.v. route simply because their mast cells lack sufficient endogenous IgE to prevent or mask their surface receptors from interacting with these drugs (Watkins, Wild and Clarke, 1985). Further studies are in progress, but we can state that the low IgE concentrations are "inherited", apparently in a manner similar to atopic IgE concentrations, and that the situation is biased towards the female (compare incidence of female reactions to anaesthetics with those in males). It would be advisable to enter this fact upon the patient's notes rather than the negative comment "not consistent with allergy or atopy", since we are not necessarily contemplating an allergic mechanism.

Some type of in vivo *assessment is essential* and common practice in Europe involves intradermal testing (Fisher, 1979, 1984a). Suitable dilutions of the test drugs (1:1000; 1:10000 and perhaps 1:100000) in saline are injected intradermally (0.1 ml) to the anterior surface of the forearm. It has recently been suggested that this injection volume is too great (Fisher, 1984a) and leads to false positives, but with adequate controls this is really not a problem. Dilute histamine solution is used as a control. A positive result (fig. 2) is a weal at least 1 cm in diameter which lasts for more than 30 min. Unfortunately many drugs, and particularly neuromuscular drugs (e.g. tubocurarine and atracurium), produce an extremely high incidence of false positives (Wood et al., 1985) so that what

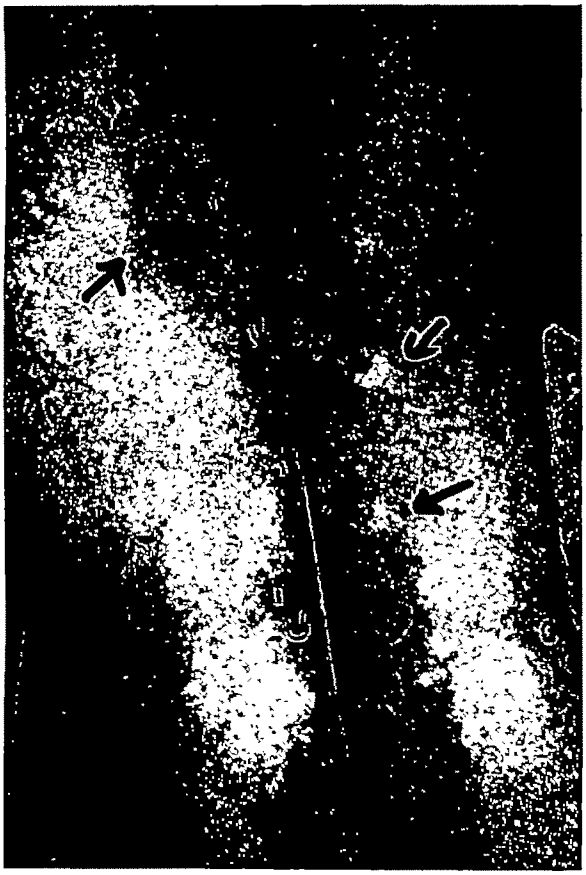

FIG. 2. Skin testing with anaesthetic drugs. Genuine hypersensitivity response to suxamethonium. Intradermal test (left arm) shows two positive weals (arrowed) to suxamethonium at dilutions of 1:1000 and 1:10000, respectively. Prick or scratch test (right arm) positive weal (arrowed) at 1:10 dilution. The presence of circulating IgE antibodies to this drug was confirmed by other tests, including a specific RAST test.

is a simple test to perform requires considerable expertise to interpret correctly. The positive artefacts may reflect the pharmacological properties of the drugs and the chemical arrangement of their active groups (Assem, 1984), rather than their immunogenicity. The author prefers scratch or prick tests, the conventional allergen test procedure of the dermatologist. Higher concentrations of the test substances are required (e.g. 1:10). Positive results by this procedure should be accepted as confirmation of a specific drug reaction (fig. 2). Unfortunately, the prick test is rather insensitive and probably misses as many genuine reactions as the intradermal test overestimates. It is strongly recommended that both intradermal and prick tests are carried out simultaneously on the patient's arms. In the absence of standardized RAST tests to specific anaesthetic drugs, these tests are certainly the best available.

Theoretically, although such tests themselves constitute possible patient sensitization and a potential cause of immediate and life-threatening anaphylactic shock, in practice no testing laboratory has ever reported serious responses. Nevertheless, full recovery facilities must be available.

Passive transfer tests find little use in the U.K. The reasons are multiple: a lack of sensitivity and poor negative predictive value, a risk of hepatitis in humans (Prausnitz–Küstner, PK tests) or a need for animal facilities for passive cutaneous anaphylaxis (PCA), or PK tests. The immunological principles behind such assays may be found in any standard immunology textbook.

The Benveniste test (human basophil degranulation test) is not invasive and may be carried out directly on the haematology samples taken at the time of the incident. It concerns the specific activation, and destruction, of blood basophils and as such can be tested for at any convenient time by challenge of the various drugs against the patient's isolated and basophil-enriched leucocytes (Theobald-Segalen et al., 1982).

RECOMMENDED MINIMUM PROCEDURE

The following are the recommendations of the Sheffield based national adverse anaesthetic reaction advisory service (NAARAS). It cannot be emphasized too strongly that a successful investigation requires the co-operation of all involved: the anaesthetist and possibly the surgeon, the clinical immunologist, the dermatologist or allergologist and finally, but certainly not least, the patient.

Suggested Procedure

Immediate period

(1) As soon as convenient, the anaesthetist takes duplicate 5-ml EDTA blood samples. These immediate samples are followed by further samples taken 1, 3, 6, 12 and 24 h later, or at some convenient approximation of these times.

(2) At some stage after the reaction is under control, the anaesthetist should telephone the referral immunology laboratory, discuss the case briefly and ensure that the correct samples and documentation will be made.

(3) One set of blood samples are analysed at the

base hospital for complete blood profiles, including cell differential counts.

(4) Plasma is separated from the other sets of samples as soon as possible and stored at −20 °C until despatched to the immunology laboratory together with documentation (5).

(5) The anaesthetist provides a full account of the reaction and relevant clinical background. A "yellow card" adverse reaction notification should be sent to the Committee on Safety of Medicines (CSM).

The immunology laboratory

(6) Analyses the plasma sample and interprets the results in terms of the supplied case history.

(7) Arranges skin tests with the dermatology department at some time convenient to everyone, including the patient.

Communication of conclusions

(8) On the basis of the case history and laboratory tests, including the initial haematological profiles, a conclusion is reached regarding both the probable mechanism and the causative agent(s).

(9) These conclusions are communicated *in writing* to the anaesthetist concerned and to the patient's own doctor. *Safer drug combinations or alternative anaesthetic regimens are suggested.*

(10) The situation is explained to the patient, who should be advised at all times to carry some warning of the risk of anaesthetic reaction, together with suggestions for emergency drug combinations and alternative anaesthetic procedures.

CONCLUSIONS

There are numerous reviews in the literature concerning anaesthetic reactions, their frequency, investigation and future prophylaxis. The reader who wishes to pursue this topic in detail is referred to Watkins and Salo (1982), Fisher (1984b) and Sage (1985).

It cannot be stressed too highly that all clinical adverse events in the U.K. must be reported to the CSM via the familiar "yellow card". In this way, important patterns of drug reactivity emerge. However, such reporting does not help the *individual patient* and the procedures discussed in this paper should be considered as complementary to such yellow card reporting in providing a diagnosis of mechanism and causative agent in the individual. Even when patients have not been subjected to immediate laboratory investigation, a relatively simple examination of blood serology and skin tests even weeks after the event may still establish useful pointers to their future clinical management.

In the past there has been a tendency to regard adverse reactions, particularly anaphylactoid reactions in anaesthesia, as rare occurrences in high-risk surgical patients. This is far from the case, and this Unit investigates several deaths each year involving minor "routine" surgery in previously healthy young people. In a recent review Chaplin (1986) made the same point in reporting on the growing number of legal actions for deaths under anaesthesia and on the numbers of irreversibly brain-damaged patients in West Germany. The major causes appear to be similar to those reported in the U.K. mortality study by Lunn and Mushin (1982). Nevertheless, many anaesthetic reactions do resemble those produced by immediate hypersensitivity type mechanisms and laboratory analysis is the only way to distinguish avoidable (human error) from unavoidable hypersensitivity response. In fairness, it must be pointed out that many extremely useful drugs have peculiarities which at first sight may seem alarming, for example skin histamine-releasing properties resulting in exaggerated flushing. Subjective individual reporting without laboratory follow-up could well result in the loss of the drug from the market, which would be to no advantage to patients, and ultimately will discourage the development of better and safer drugs by the pharmaceutical industry.

ACKNOWLEDGEMENT

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DRUG INTERACTIONS IN ANAESTHESIA

M. J. HALSEY

Drug interactions in anaesthesia were reviewed more than 10 years ago (Grogono, 1974) and more recently have been the subject of short chapters in textbooks (Dundee and McCaughey, 1980; Thornton, 1981). One of the best general reviews on drug interactions from the point of view of clinical pharmacology was written by Prescott in 1973, but this contained very few examples of drugs used in anaesthesia. The traditional approach to the topic either classifies the interactions on the basis of where they occur in the body or, alternatively, lists the anaesthetic and additional drugs with an outline of the adverse reactions that may be encountered. It did not seem very profitable for the present review solely to update such tables of interactions; instead an alternative approach has been attempted which is particularly relevant to anaesthesia—namely to consider drug interactions in terms of two broad classes of underlying mechanisms: pharmacodynamics and pharmacokinetics. Pharmacodynamics describes the relationships between drug concentration and drug response; pharmacokinetics describes the relationships between the rates of change of drug concentrations in the different parts of the body.

The *pharmacodynamic* interactions occur between drugs with similar or opposite pharmacological effects or "side effects". The underlying mechanisms include competition at molecular or cellular sites of action. The effects are generally common to related drugs. The *pharmacokinetic* interactions occur when one drug alters the absorption, distribution, metabolism or excretion of the other drug. As will be seen, this type of response varies between patients without any particular drug pattern and is difficult to predict. Mechanisms include altered protein binding, enzyme induction and inhibition and impaired renal clearance. Examples of both of these classes of drug interactions occur with the volatile anaesthetics.

Potential clinical importance

There has sometimes been a tendency to overemphasize the clinical importance of drug interactions. Any response that is potentially lethal (such as those associated with oral anti-coagulants, hypoglycaemic agents and cytotoxic drugs (Prescott, 1973)) is of undisputed importance. However, other interactions (such as the interaction of local anaesthetics and sulphonamides (Martindale, 1977)) may be equally well established, but are primarily of academic interest only.

Nevertheless, the overall potential for drug interactions is greater in anaesthesia than among other areas of medicine, for three reasons. First, the patient who is being considered for anaesthesia may be already receiving several drugs. It has been reported that patients in one London hospital are receiving concurrently five to six drugs, while one patient in every 10 receives 10 drugs at the same time. The supreme example was from another hospital when one patient was given 41 drugs during a single admission (Prescott, 1973). A wider perspective on the problem as related to anaesthesia was provided by the multicentre study on isoflurane (Levy, 1984). This included specific questions about concurrent medical therapy related to digitalis, beta-blockers, diuretics, nitrates and bronchodilators as well as recording any history of smoking (fig. 1). However, it should be noted that these data provide an estimate only of the minimum drug usage in this particular group of patients, because other types of drugs were not listed on the questionnaire.

The second reason for anaesthetists being more aware of the potential problem is that, even if the patient has no concurrent drug therapy, he may receive as many as 9 or 10 drugs as part of his anaesthetic regimen. These might include, for example: an opioid or tranquillizer, and atropine

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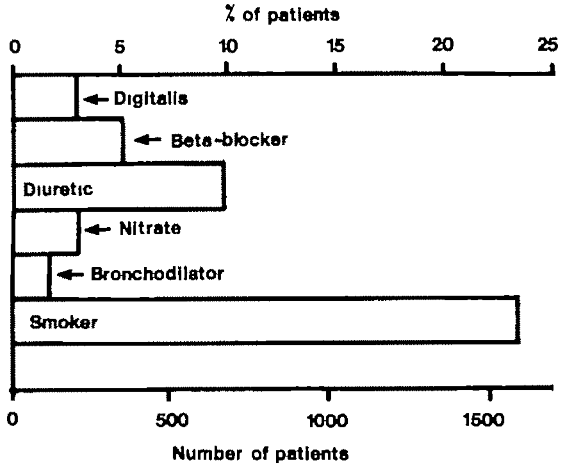

FIG. 1. The incidence of preoperative medications in the multi-centre clinical trial of isoflurane. Only the five groups of drugs and smoking were recorded. (Reproduced, with permission, from Levy (1984).)

as preanaesthetic medication; a barbiturate for induction; suxamethonium for intubation (with lignocaine spray or gel on the tube); nitrous oxide, oxygen and a volatile agent (or synthetic opioid) for maintenance of anaesthesia; another neuromuscular blocking drug during the operation and finally a "reversal" agent such as neostigmine (with atropine). Although such polypharmacy would not necessarily be recommended, it should be noted that, not only do several drug interactions occur between the different types of drugs, but also the anaesthetist utilizes the predictable synergism or antagonism as part of his anaesthetic technique.

The third reason for being concerned about drug interactions in anaesthesia in particular is that the majority of the responses are associated with acute depression of the nervous system and the inhibition of protective reflexes. Without any intervention the results are potentially catastrophic, and long term consequences may occur when the patient is not being intensively monitored.

Additivity of drug responses

Many actions of closely related drugs in anaesthesia are additive rather than synergistic or antagonistic. The distinction is important, in that the former effect is not a drug interaction as formally defined. Thus the apparent effects of one drug can be increased or decreased by the previous or concurrent administration of another agent. However, the essential evidence for a drug interaction is that the results of such a combination are different from the sum of the effects of the two drugs given separately; the difference can be either quantitative or qualitative, and allowance must be made for the shapes of the dose–response curves.

It has generally been thought that, when two gaseous anaesthetics are administered together, their anaesthetic effects are additive. However, most of the clinical studies quoted in support of this statement only demonstrate that the use of the second agent (such as nitrous oxide) reduced the requirement of the first (such as halothane). This reduction in requirement may have been either exactly that predicted from the individual potencies (i.e. additivity) or a greater or lesser reduction (i.e. synergism or antagonism respectively). It was not until the anaesthetic potency (MAC) of nitrous oxide on its own was determined in a clinical study under hyperbaric conditions (Hornbein et al., 1982) that it was possible to test *directly* the additivity of its combination as determined in much earlier studies with halothane (Saidman and Eger, 1964), fluroxene (Munson, Saidman and Eger, 1965), methoxyflurane (Stoelting, 1971), enflurane (Torri, Damia and Fabiani, 1974) or isoflurane (Stevens et al., 1975) (fig. 2). It was found, for example, that 50 % of the nitrous oxide minimum alveolar concentration (MAC)

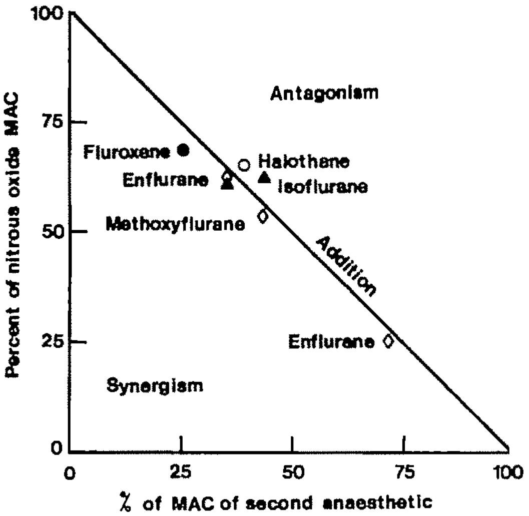

FIG. 2. The percentage of MAC of nitrous oxide when combined with the percentage of MAC of the second agent that produces immobility in 50% of the patients. All these drugs have anaesthetic potencies which are effectively additive. (Reproduced, with permission, from Eger (1985).)

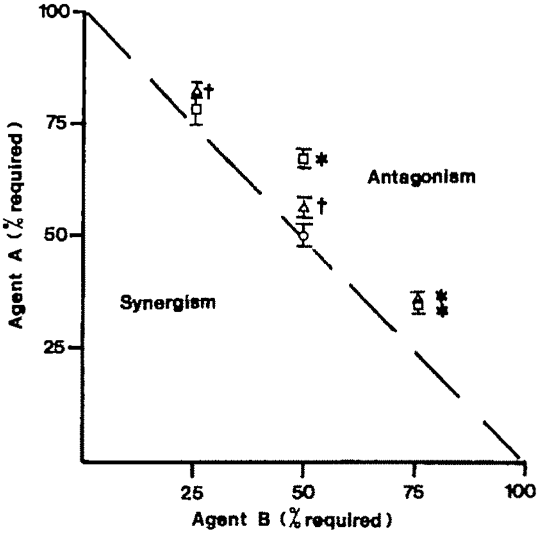

FIG. 3. The relative potencies of mixtures of: methohexitone and nitrous oxide (□); Althesin and nitrous oxide (△); thiopentone and propanidid (○). The potencies of the combinations are expressed relative to those of the agents alone (*$P < 0.001$; †$P < 0.01$). (Reproduced, with permission, from Wardley-Smith and Halsey (1985).)

plus 50% of the MAC of the second anaesthetic was equal in anaesthetizing effect to that of 100% MAC of either agent alone. In figure 2 there are some variations from the strict line of additivity, which in the case of isoflurane appear to depend on the ages of the patient groups being studied, but these variations are not statistically significant. Thus the anaesthetic effects of these drugs, although different in the combinations, are not indicative of drug interactions.

In contrast, mixtures of inhalation and i.v. anaesthetics do not universally have additive potencies. It has been known for some time that nitrous oxide appears to be antagonistic to ketamine anaesthesia: 67% nitrous oxide decreases ketamine requirements by only 40% in man (Wessels, Allen and Slogoff, 1973). A systematic quantitative study in animals (fig. 3) has revealed that a combination of nitrous oxide and Althesin or of nitrous oxide and methohexitone is antagonistic, whereas that of thiopentone and propanidid is not (Wardley-Smith and Halsey, 1985). The latter study was initiated as a test of the multi-site hypothesis of the molecular mechanisms of anaesthesia (Halsey, Wardley-Smith and Green, 1978), and the magnitude of all these drug interactions indicates that such variations are of academic rather than clinical importance.

The additivity of the anaesthetic potencies of nitrous oxide and volatile agents (fig. 2) might suggest that there were no drug interactions of any kind between these agents. However, in contrast to the anaesthetic potency studies, the cardiovascular and respiratory effects of mixtures of these agents are very complex. One of the questions in the early clinical studies with isoflurane was whether its marriage with nitrous oxide would be for better or for worse? It was known that isoflurane on its own could produce depression of both ventilation and arterial pressure (Cromwell et al., 1971; Stevens et al., 1971). Since the addition of nitrous oxide to another cardiorespiratory depressant, halothane, attenuates such effects (Hornbein, Martin and Bonica, 1969), it was possible that nitrous oxide would produce similar changes towards awake values during isoflurane anaesthesia. In volunteer studies, under controlled ventilation conditions and at equivalent values of MAC, nitrous oxide did produce a 10–25% increase in mean arterial pressure. Nitrous oxide does have effects on its own, but the result of the combination with the volatile agent is not simple additivity. In contrast, in an additional study when the patients were allowed to breathe spontaneously, nitrous oxide failed to reverse the respiratory depression seen with isoflurane alone (Dolan et al., 1974). These two sets of data are part of the mass of clinical information about the combination of the two agents which indicate a spectrum of underlying drug interactions. The picture is complicated by apparent conflicts between the data of different studies. For example, another investigation (Eger et al., 1972) is sometimes quoted as evidence for nitrous oxide attenuating the respiratory depression of isoflurane. However such a conclusion is questionable, since the groups of patients in that particular study were different in other ways (especially age). The complexities of such clinical data mean that it is not very profitable to attempt to dissect out underlying drug interactions and better examples of the topic are to be found in more precisely defined physiological responses such as those discussed in the rest of this review.

PHARMACODYNAMIC INTERACTIONS

Catecholamines

It is well established that halothane causes arrhythmias and sensitizes the myocardium to the effects of both endogenous and exogenous cate-

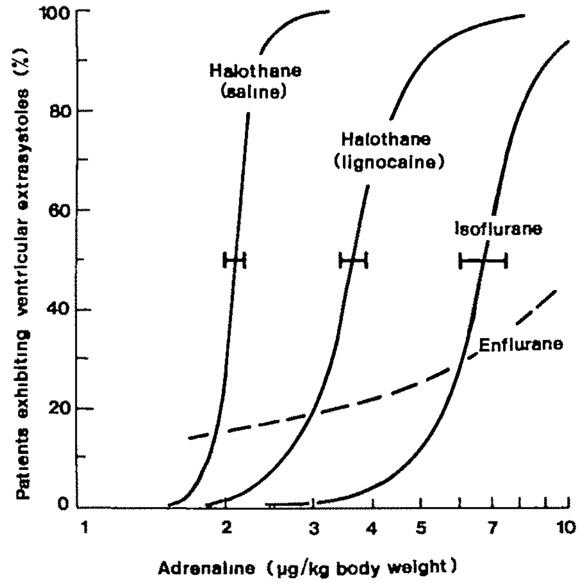

FIG. 4. The arrhythmogenicity of adrenaline determined in patients anaesthetized with 1.25 MAC of enflurane, halothane or isoflurane in oxygen. The effect of halothane was tested with or without lignocaine. (Reproduced, with permission, from Johnston, Eger and Wilson (1976).)

cholamines. Various reports indicate an incidence of ventricular arrhythmias of 3–7% without or with exogenous adrenaline (Katz, Matteo and Papper, 1962; Reisner and Lippmann, 1975). This incidence increases with increase in $P\text{CO}_2$. A direct comparison is often made between halothane, enflurane and isoflurane in this type of drug interaction (fig. 4). At first sight it would appear that isoflurane does not interact with adrenaline. However, a closer examination of the numerical data (table I) indicates that enflurane, rather than isoflurane *may* produce the least potentiation. The ED$_{50}$ was defined by the investigators as the concentration of adrenaline injected submucosally which produced three or more ventricular extrasystoles in 50% of the patients. On the other hand, the threshold concentration is the lowest concentration at which any patient developed arrhythmias. This threshold concentration can be increased two- to three-fold by the addition of 0.5–1% lignocaine to the adrenaline in the case of halothane and enflurane. The effect of lignocaine on adrenaline threshold concentration in the presence of isoflurane has not been determined.

TABLE I. *Adrenaline doses associated with arrhythmias. (Data from Johnston, Eger and Wilson (1976) and Horrigan, Eger and Wilson (1978))*

Agent	Arrhythmic threshold dose (µg kg^{-1})	ED$_{50}$ dose (µg kg^{-1})
Halothane	1.8	2.1
Isoflurane	5.4	6.7
Enflurane	3.6	10.9

The only method of demonstrating unequivocally that there is or is not a drug interaction is to determine the effects of the two drugs separately and then combined together. The arrhythmic threshold following infusion of adrenaline to unanaesthetized man has not been determined adequately. However, the analagous experiment in animals indicates that isoflurane at 1.25 MAC reduces control adrenaline arrhythmic doses by as much as 40% (Joas and Stevens, 1971), although scatter of the data in the awake control group prevented this decrease from being statistically significant.

Catecholamine–anaesthetic drug interactions are clearly clinically relevant, but it should be noted that the site of administration is as important as the dose of adrenaline injected (Cotton et al., 1986). In our hospital, surgeons administer up to 500 µg of adrenaline during certain operations (Nunn, 1985) and in a 70-kg man the resulting dose (7.1 µg kg^{-1}) is certainly within the range of potential problems in some patients (table I). An example of endogenous release of adrenaline occurs during surgery for the removal of phaeochromocytoma. Isoflurane anaesthesia, without any anti-arrhythmic drugs, has been successfully used and has not produced any ventricular arrhythmias despite a demonstrable increase in adrenaline concentrations (Suzukawa et al., 1983).

Neuromuscular blocking drugs

The inhalation anaesthetics cause a dose-related potentiation of the actions of neuromuscular blockers. The anaesthetics themselves have blocking effects, as revealed by the impairment of the ability to sustain a response to high frequencies of tetanic stimulation (160–200 Hz) (Miller et al., 1971a,b). Studies with a wider range of anaesthetics at higher concentrations using the rat phrenic nerve–diaphragm preparation revealed that there were no noticeable effects on twitch height until concentrations were at least twice those required for the maintenance of anaesthesia (Pollard and Millar, 1973). However, at the higher concentrations there was a striking difference

TABLE II. *Neuromuscular blocker potentiation. Doses of neuromuscular blockers that depress twitch height by 50% at 1.25 MAC of the agents in man expressed in each case relative to halothane. (Data from Miller, Way et al. (1971), Miller, Eger et al. (1971), Fogdall and Miller (1975) and Rupp, Miller and Gencarelli (1984))*

Blocker	Halothane	Enflurane	Isoflurane
Tubocurarine	1	0.29	0.30
Pancuronium	1	0.59	0.55
Gallamine	1	—	0.42
Suxamethonium	1	0.96	0.67
Vecuronium	1	0.76	0.87

between the anaesthetics. Diethyl ether, methoxyflurane and trichloroethylene caused a depression of twitch height at all concentrations; cyclopropane caused potentiation at all concentrations, while halothane and chloroform caused potentiation at lower concentrations and depression at higher concentrations. It is clear that the effects of the anaesthetics on the neuromuscular junction are complex, although under clinical conditions very little apparent effect is observed when the agents are used alone. However, the drug interactions between the neuromuscular blocking agents and inhalation anaesthetics are now widely recognized. Smaller doses of blocking agents are required for equivalent blockade during enflurane and isoflurane anaesthesia than during halothane anaesthesia (all at equi-MAC conditions). Furthermore, increasing alveolar concentrations of all the agents decrease the amount of neuromuscular blocking drug needed (Miller et al., 1972). The dose-dependent degree of enhancement of blocking effects differs between the different agents and sometimes between the different anaesthetics with the same blocker. For example, the effect of increasing the halothane concentration on tubocurarine requirement is much more dramatic than the equivalent effect with isoflurane. Thus the ranking order of dose dependencies is different from that of agent dependencies. On the other hand, the effects of increasing halothane or isoflurane concentrations on pancuronium requirement appear to parallel each other (Miller et al., 1972). It is potentially misleading to compare relevant doses at only one anaesthetic concentration but, in order to provide a general comparison, table II indicates the relative effects at 1.25 MAC.

Table II does not imply that halothane itself has no potentiating action. For example, the dose of tubocurarine required during halothane anaesthesia is 70% of that required during nitrous oxide–barbiturate–narcotic anaesthesia (Ali and Savarese, 1976). There is no effect of the duration of anaesthesia on the potentiation of tubocurarine by halothane (Miller, Crique and Eger, 1976) but, unexpectedly, potentiation by enflurane of this drug is time-dependent. Paralysis with tubocurarine under enflurane anaesthesia increased at a rate of 9±4% per hour, despite a constant blood concentration of the neuromuscular blocking agent (Stanski, Ham and Miller, 1979). This may relate to the different mechanisms by which the different anaesthetics augment the blocking action and it is probable that more than one site (e.g. neuromuscular junction and skeletal muscle) is involved.

A series of mechanisms have been proposed to explain the differences in anaesthetic potentiation of neuromuscular blocking actions. *In vitro* studies (Vitez et al., 1974; Chaudry, Ohta and Nagashima, 1980) demonstrated that the relative potentiation was enflurane > halothane = isoflurane. Thus *in vivo* differences between halothane and isoflurane may be related to differences in regional blood flow allowing a greater fraction of injected agent to reach a particular site of action rather than to inherent differences in sensitivity at the sites. This would, of course, be an example of a pharmacokinetic interaction, but the neuromuscular blocking drug interactions are included in the pharmacodynamic class because it has been demonstrated unequivocally that halothane decreases the steady state plasma concentration of tubocurarine required to produce a 50% blockade of neuromuscular function (fig. 5). These data (Stanski et al., 1979) incidentally demonstrate the decreased variability in the response in the presence of the drug interaction with halothane which appears to be one of the characteristics of this type of pharmacodynamic mechanism.

The clinical implications are that smaller doses of myoneural blockers are needed to give satisfactory operating conditions during enflurane and isoflurane anaesthesia than with other anaesthetic techniques. This has the advantage that, when the appropriate amount of blocker is used, neuromuscular activity returns to normal more quickly at the end of an operation using enflurane or isoflurane anaesthesia when the administration of the volatile agent is discontinued.

The demonstration (Rupp, Miller and Gencarelli, 1984) that the order of potency potentiation for vercuronium (enflurane > isoflurane > halo-

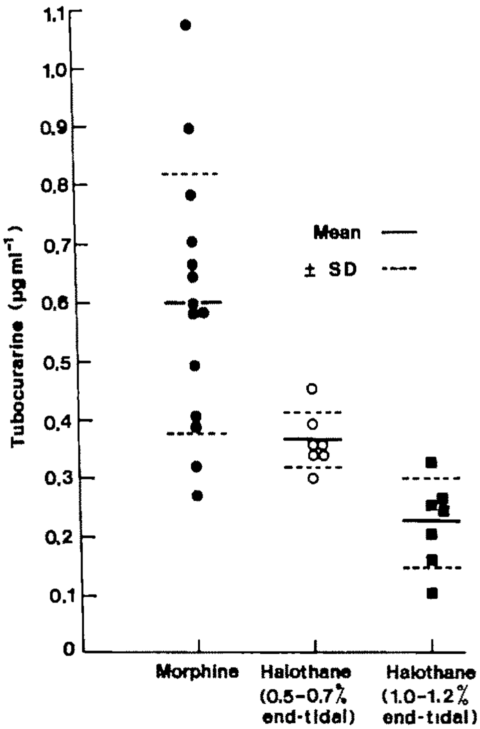

FIG. 5. The steady state plasma concentrations of tubocurarine required to produce a 50% blockade of neuromuscular function during morphine–nitrous oxide anaesthesia compared with halothane–nitrous oxide anaesthesia (at two different concentrations of end-tidal halothane). (Reproduced, with permission, from Stanski and colleagues (1979).)

thane) is different from that produced for pancuronium or tubocurarine raises the possibility of a spectrum of interactions. The other new neuromuscular blocking drug is atracurium, which has been studied in patients anaesthetized with halothane (Payne and Hughes, 1981), enflurane (Ramsey et al., 1982) and isoflurane (Sokoll et al., 1983). Because of the experimental differences between the studies, it is not appropriate to compare quantitatively the interactions with these agents. However, in a comparison with "balanced" anaesthesia (nitrous oxide and fentanyl) it was found that both enflurane and isoflurane potentiated the effect of atracurium: with the volatile agents, patients required approximately 50–75% of the dose of atracurium to attain a given degree and duration of block (Sokoll et al., 1983).

Finally, the volatile agents modify the characteristics of suxamethonium neuromuscular blockade. With prolonged administration of suxamethonium the transition from phase I (depolarizing) blockade to phase II (non-depolarizing) blockade occurs at a lower cumulative dose of the blocker during nitrous oxide–halothane, nitrous oxide–enflurane and nitrous oxide–isoflurane compared with nitrous oxide–narcotic (Hilgenberg and Stoelting, 1981; Donati and Bevan, 1983a). This phenomenon has been demonstrated with both intermittent bolus injections of suxamethonium and continuous infusion of the agent (Donati and Bevan, 1982).

It has been argued that the rapidity of onset of phase II blockade seen with inhalation anaesthetic agents is a disadvantage, because suxamethonium can only be administered for a short time (Hilgenberg and Stoelting, 1981). The alternative view is that inhalation agents appear to have many advantages when used with suxamethonium (Donati and Bevan, 1983a); because of its reversibility with anticholinesterase agents (Donati and Bevan, 1982) phase II blockade does not need to be avoided. Furthermore, although the characteristics of the blockade generally change later with nitrous oxide–narcotic anaesthesia, this change is less predictable than with isoflurane. As a result, if one tried to determine a "safe" period during which phase II blockade does not occur in most patients, it would not be much different with either form of anaesthesia. Finally, a rapid transition from phase I to phase II blockade, as seen with inhalation agents, can minimize the occurrence of "mixed" blockade, for which anticholinesterases are poorly effective. A recent study has demonstrated that isoflurane not only accelerates the onset of the phase II blockade, but also potentiates its intensity (Donati and Bevan, 1983b). This, of course, is similar to the effects with other neuromuscular blocking agents, although the relationships between a phase II blockade and a non-depolarizing blockade are not yet clear mechanistically.

Calcium antagonists

Although calcium antagonists were discovered more than 20 years ago, it is only in the past few years that their potential interactions with anaesthetics have started to be systematically investigated. It has been argued that the anaesthetics themselves may be considered to be non-specific calcium antagonists (Jones, 1984), while it is now clear that particular calcium entry blockers have unique haemodynamic effects. For example, in the presence of halothane, nifedipine decreases systemic vascular resistance, while verapamil decreases cardiac output (Kates et al., 1984). It is not yet clear whether such effects are simply additive or involve specific drug interactions. The differences in both magnitude and concentration dependence of the depressant effect of verapamil in the presence of enflurane or isoflurane (fig. 6) suggest that drug interactions may prove to be more important than has previously been thought (Reves, 1984).

More unequivocal evidence for drug interactions between calcium antagonists and anaesthetics has now been demonstrated for their central nervous system effects as distinct from their cardiovascular actions. In rodent studies, nitrendipine, flunarizine and verapamil significantly increased anaesthetic potencies of pentobarbitone and ethanol as measured by the loss of righting reflex (Dolin and Little, 1986). These calcium antagonists, even at doses up to 10 times greater than those used to determine the anaesthetic potency changes, did not themselves produce a state of anaesthesia. Possible pharmacokinetic mechanisms appear to have been excluded and, if such interactions do prove to occur also in man, the clinical implications could be as interesting as the mechanistic implications.

PHARMACOKINETIC INTERACTIONS

Anaesthetic metabolism

This type of drug interaction is associated with the rate of change of either the anaesthetic or some toxic product produced by biotransformation of the agent. The resulting concentration of the toxic substance is dependent on both its rate of formation, rate of deactivation and rate of excretion. Little is known about the pharmacokinetics of the latter processes, but the rate of formation is clearly linked to enzyme induction or inhibition. Enzyme induction is produced by prior treatment with drugs or by chronic exposure to environmental chemicals. Enzyme inhibition can be produced in the experimental situation by a variety of drug treatments and has been covered in another review (Davie, 1977).

It has been argued that the majority of drug interactions associated with enzyme induction do not have major effects on the conduct of anaesthesia (Mazze, 1984), but there are definite patients for whom ignoring the potential for anaesthetic metabolism could prove fatal.

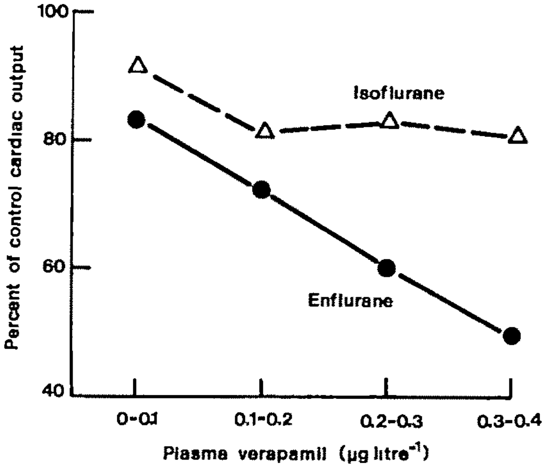

FIG. 6. Depressant effects of verapamil on cardiac output during 1 MAC of isoflurane or enflurane anaesthesia in dogs. (Data from Kapur, Flacke and Olewine (1982). Figure reproduced, with permission, from Eger (1984).)

The first example is halothane hepatitis. The link between halothane anaesthesia and liver damage has been reviewed again recently (Neuberger and Williams, 1984; Brown and Gandolfi, 1987). Studies of the mechanisms of halothane hepatitis have shown how differences in drug metabolism may interact with individual variations in immune responses to determine the type of liver injury. Animal models have shown one form of direct hepatotoxic effect of halothane which is dependent on enzyme induction either with polychlorinated biphenyls (at one stage an industrial pollutant) or with phenobarbitone pretreatment followed by administration of halothane with limited cellular oxygen supply. Clinical studies have shown that patients with severe hepatic necrosis following halothane administration have circulating antibodies reacting with altered liver cell membrane determinants, which are generated by the oxidative route of metabolism (Neuberger et al., 1981). The evidence for the immunological hypothesis of the mechanism of halothane hepatitis is now quite strong, but there seems the possibility that the observed alterations in immunological sensitivity may be the result of this particular type of liver injury, rather than the cause of it. The final elucidation of the mechanisms is still awaited, but at the moment all the postulates include a role for enzyme induction (to a greater or lesser extent). In this example the drug interaction is changing qualitatively the type of response, rather than having only a quantitative effect.

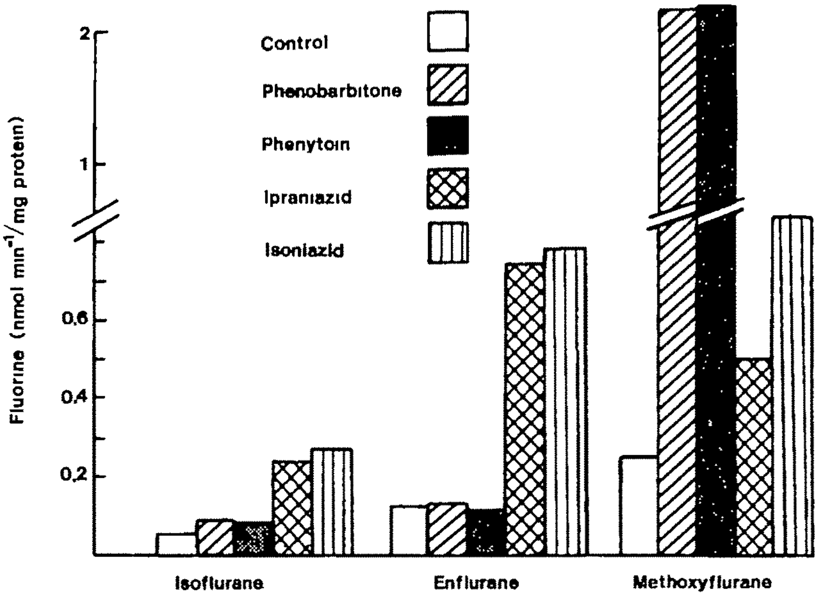

FIG. 7. Microsomal defluorinase activity in hepatic microsomes from rats pretreated with various drugs and then exposed to isoflurane, enflurane or methoxyflurane. (Reproduced, with permission, from Eger (1984).)

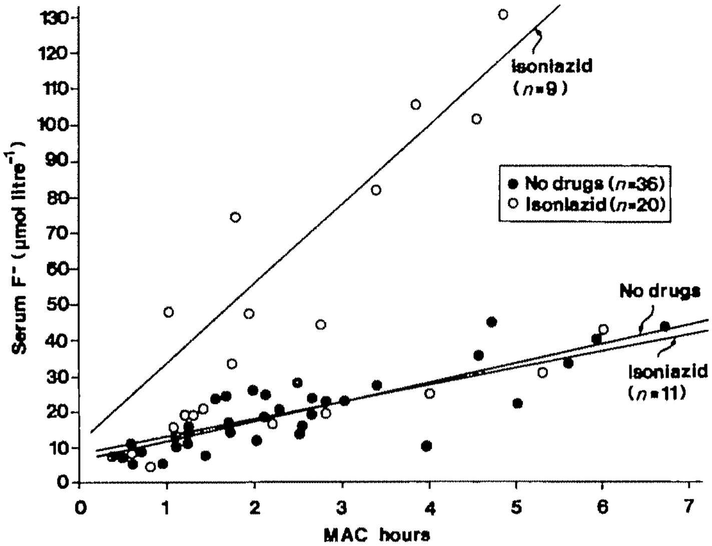

FIG. 8. Peak serum fluoride concentrations following enflurane anaesthesia; some of the patients were also being treated with isoniazid. (Reproduced, with permission, from Mazze, Woodruff and Heerdt (1982).)

A second example of anaesthetic metabolism is provided by the defluorination of the volatile anaesthetics (fig. 7). The animal data demonstrate first that there is a considerable difference between the agents in their responses to enzyme induction following pretreatment with specific drugs. More interestingly, the optimum enzyme inducing agent for one anaesthetic is not the same for another. In general, it appears that the overall order of susceptibility to enzyme induction is related to the ease of biotransformation in the untreated animals. It is not possible to extrapolate quantitatively from

TABLE III. *Cross-index of references to drug interactions with volatile anaesthetics*

	Halothane	Enflurane	Isoflurane	Comment
Adrenaline	Katz et al (1962) Forbes (1966) Snow et al (1968) Joas and Stevens (1971)	Konchigeri et al (1974) Lippman and Reisner (1974) Johnston et al (1976) Horrigan et al (1978)	Joas and Stevens (1971) Tucker et al (1974) Johnston et al. (1976)	Sensitization of arrhythmic potential (see table I)
Aminophylline	Roizen and Stevens (1978)			Ventricular tachycardia
Amitriptyline		Sprague and Wolf (1982)		Potentiation of seizure activity
Atracurium	Payne and Hughes (1981)	Ramsey et al. (1982)	Sokoll et al (1983)	Potentiation
Atropine			Valentia et al (1983)	Tachycardia
Gallamine	Miller, Way et al (1971)		Miller, Way et al (1971)	Potentiation (see table II)
Isoniazid		Mazze et al. (1982)		Enzyme induction
Imipramine	Edwards et al. (1979)	Edwards et al (1979)		Tachyarrhythmias with halothane
Ketamine	Bidwai et al (1975)	Bidwai et al (1975)		Cardiovascular depression, particularly with halothane
Metaraminol	Tucker et al (1974)		Tucker et al (1974)	Arrhythmogenic potential reduced with isoflurane
Metoprolol		Morr-Strathman et al (1981)		No cardiovascular contraindications
Monoamine oxidase inhibitors	Perks (1964)			Anaesthetics potentiated
Nifedipine	Fahmy and Lappas (1983)			Additive actions
Nitrous oxide	France et al (1974)		Dolan et al. (1974) France et al (1974)	Both cardiovascular and respiratory interactions
Ouabain		Ivankovich et al (1976)	Ivankovich et al (1976)	Increased tolerance
Pancuronium	Miller, Way et al (1971)	Fogdall and Miller (1975)	Miller, Way et al (1971)	Potentiation (see table II)
Phenylephrine	Tucker et al (1974)		Tucker et al (1974)	Arrhythmogenic potential less with isoflurane
Propanolol	Kaplan and Dunbar (1976) Philbin and Lowenstein (1976) Reves et al (1981)	Kaplan and Dunbar (1976) Horan et al (1977a) Reves et al. (1981)	Philbin and Lowenstein (1976) Horan et al. (1977b)	Only potential contraindications
Sodium nitroprusside	Eltringham et al. (1982)	Bedford (1979) Eltringham et al. (1982)		Potentiation of hypotension with enflurane
Suxamethonium	Miller, Way et al. (1971) Vitez et al (1974) Hilgenberg and Stoelting (1981)	Fogdall and Miller (1975) Hilgenberg and Stoelting (1981) Donati and Bevan (1982)	Miller, Way et al. (1971) Vitez et al (1974) Donati and Bevan (1983a) Donati and Bevan (1983b)	Potentiation (see table II)
Tubocurarine	Miller, Eger et al (1971) Miller et al (1972) Vitez et al (1974)	Fogdall and Miller (1975) Stanski et al. (1979)	Miller, Eger et al (1971) Miller et al (1972) Vitez et al. (1974)	Potentiation (see table II)
Vecuronium	Rupp et al (1984)	Rupp et al (1984)	Rupp et al (1984)	Potentiation (see table II)
Verapamil	Hantlar et al (1983)	Hantlar et al (1983)	Hantlar et al (1983)	Potentiation of sinus node function

such *in vitro* animal derived data to *in vivo* biotransformation.

One of the most interesting clinical studies of enzyme induction has been with isoniazid. There appears to be a bimodal distribution in the response, with isoniazid pretreatment enhancing defluorination in only nine of 20 subjects studied (fig. 8). It has been postulated that this difference may be related to the distribution of slow and rapid acetylators of isoniazid which is known to exist in the normal population. The acetylation of isoniazid results in the formation of hydrazine, which in turn induces formation of cytochrome P451, which leads to enhanced enflurane defluorination. Thus this example of a drug interaction is the result of biotransformation of the drug, which in turn alters the biotransformation of the other drug. The result is more than academically interesting, because the result in some cases is a serum fluoride concentration increased to more than 100 μmol litre^{-1}, which has definite nephrotoxic potential.

CONCLUSION

This review has concentrated on specific examples of drug interactions in anaesthesia, which have been divided into those which are based on pharmacodynamic mechanisms and those which are related to pharmacokinetic mechanisms. This distinction maybe useful because pharmacodynamic interactions predominate between those drugs which have related pharmacological effects and it appears that one of the characteristics is a decreased variability in patient response. If this hypothesis proves correct in general, and the majority of pharmacodynamic interactions result in a decreased biological variability, the clinical implications could be at least as important as those of the interactions themselves. In contrast, pharmacokinetically based interactions definitely produce responses which vary widely between patients and occur between drugs which appear to be pharmacologically unrelated. As such they are difficult to predict and the clinical consequences in a few instances can be catastrophic (for example halothane hepatitis).

This review has not attempted to be comprehensive, but a table of cross references to the interactions with the volatile anaesthetics (table III) includes other drugs which may be relevant to the topic. In addition, the reviews by Sear (1987) and Hunter (1987) in this postgraduate educational issue include further examples of interactions with i.v. anaesthetics and with neuromuscular blocking drugs, respectively.

The introduction of both new volatile anaesthetics and new drugs administered concomitantly during anaesthesia has highlighted the potential importance of drug interactions. However, it should be emphasized that drug interactions in themselves are not necessarily good or bad factors. Some obviously lead to contraindications for certain circumstances; others—like the potentiation of neuromuscular activity—can actually be an advantage if the drugs are used appropriately. It is hoped that this review has emphasized the considerable importance of drug interactions in clinical anaesthesia. Knowledge of the basic interactions must form an increasing part of the essential information on modern anaesthetics.

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PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

NEWCASTLE MEETING

JULY 4–5, 1986

(The name of the author presenting the paper is shown in bold type. *Indicates non-member.)

REDUCTION OF HYALINE MEMBRANE FORMATION BY THE USE OF HIGH PEEP

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The neonatal respiratory distress syndrome (NRDS) is a disorder associated with a deficiency of surfactant, and is characterized by patchy collapse and hypoxaemia. There are regional variations in compliance which are thought to result in an uneven distribution of ventilation. This may generate intra-regional stresses, an increase in capillary transmural pressure and eventually destruction of the integrity of the alveolar capillary membrane (Mead, Takashima and Leith, 1970). This is thought to be the pathogenesis of the characteristic hyaline membrane. Another feature of surfactant-deficient lungs is the appearance on the ascending limb of the pressure–volume curve of an inflection point, believed to represent the opening of collapsed small airspaces. We have used a lung lavage model of NRDS (Lachmann, 1980) to compare the effects of two positive end-expiratory pressures (PEEP) on the production of hyaline membrane in 16 anaesthetized and mechanically ventilated rabbits.

Lung lavage with 20-ml kg^{-1} aliquots of physiological saline was performed until the arterial Po_2 was less than 15 kPa on 100% oxygen. This resulted in an inflection point on the inspiratory limb of the pressure–volume curve at an airway pressure of 8–10 mm Hg. One group of eight animals was then ventilated with a PEEP equal to the pressure at the inflection point. The second group of eight was ventilated with a PEEP 5 mm Hg less than that at the inflection point. Animals in the high PEEP group had significantly higher Po_2 than those in the low PEEP group, but the mean survival time for each group was similar (table I). However, there was a significantly higher incidence of hyaline membrane in the low PEEP group, suggesting that the repeated opening and closing of alveolar units may be associated with an increased incidence of lung damage.

TABLE I. Pa_{O_2} *after lavage, survival times and hyaline membrane scores in animals subjected to high or low PEEP. Mean* ± *SD. Significant differences (Mann–Whitney* U *test):* *P < *0.0005;* †P < *0.0001*

	High PEEP	Low PEEP
Mean Pa_{O_2} after lavage (kPa)	57.6±9.4	9.84±3.5
Mean survival time (min)	410	388
Mean hyaline membrane score (0–4)	0.7	2.7

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PROPHYLACTIC TREATMENT OF MYOCARDIAL ISCHAEMIA BY PRIOR HAEMODILUTION WITH FLUOROCARBON EMULSIONS

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Haemodilution with the fluorocarbon-containing oxygen-transporting plasma substitute 20% Fluosol-DA (FDA) can substantially reduce myocardial tissue hypoxia after infarction (Faithfull, Erdmann and Fennema, 1985). This study investigated possible prophylactic effects of FDA haemodilution.

Two groups of five juvenile Yorkshire pigs (weight range 23.5–27 kg) were anaesthetized with sodium thiopentone i.p. and ventilated with 1.5% halothane in a 2:1 mixture of nitrous oxide and oxygen using a Minivent ventilator to achieve arterial carbon dioxide tensions between 4.7 and 6.0 kPa. Neuromuscular blockade was achieved using a continuous infusion of pancuronium bromide. The right femoral artery was cannulated and a thermodilution Swan–Ganz catheter was advanced to a pulmonary artery from the right femoral vein. All pressures were transduced (Gould Statham P23dc) and displayed on a 12-channel Grass 7D polygraph. Cardiac output was measured by thermodilution using a 3500E KMA cardiac output computer. Arterial and mixed venous blood samples were analysed on a Radiometer ABL1 acid–base laboratory and a Radiometer OSM2 haemoximeter. A mid-line thoracotomy was performed, the pericardium was opened and four 200-µm diameter, steel protected gold oxygen microelectrodes were inserted 3 mm to the myocardium of the left ventricle so as to ensure that Pm_{O_2} was obtained from both "normal" and "ischaemic" areas following occlusion of the distal third of the left anterior descending coronary artery (LAD). The output from the polarized electrodes was amplified and recorded on a Riki-Denki Recorder. The experiments were conducted in an isolated Faraday cage. Electrodes were calibrated before and at the end of the experiments and results from any electrode drifting more than 7.5% per hour were discarded.

One group of animals was bled 20 ml/kg body weight and haemodiluted with FDA. The other group served as controls. After surgical preparation the animals were ventilated with halothane in oxygen for at least 30 min before LAD occlusion. The experiments ended 3 h after occlusion. Statistical analysis was performed using paired or unpaired Student's t tests as appropriate. Statistical significance was accepted at $P < 0.05$.

Before LAD occlusion cardiac output was significantly greater and systemic vascular resistance was significantly less in the FDA group. Otherwise there were no significant differences in cardiovascular variables or oxygenation between the groups. LAD occlusion caused no significant changes in the above. Initial analysis was performed on results from the microelectrode showing the greatest percentage decrease in Pm_{O_2} over the first 1 h of occlusion; this was taken to be in the most hypoxic area of myocardium. Decreases in Pm_{O_2} were significant in the control group at 15 min after occlusion, whereas this was not seen until 45 min after occlusion in the FDA-diluted animals. Analysis of other electrodes suggested greater hyperaemic compensatory response in ischaemic border areas in the FDA treated group.

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INTRATHECAL MIDAZOLAM IN THE RAT—EVIDENCE FOR SPINALLY-MEDIATED ANALGESIA

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Subarachnoid midazolam has been shown to interrupt sympathetic reflexes evoked by stimulation of Aδ and C afferents in anaesthetized dogs (Whitwam et al., 1982) and to afford analgesia equivalent to diamorphine in anaesthetized man (Cripps and Goodchild, 1986). This study set out to provide evidence for spinally-mediated analgesia in awake rats receiving intrathecal midazolam.

Fine Portex catheters were implanted in the lumbar subarachnoid space of 10 male Wistar rats (150–350 g) under halothane anaesthesia. Rats with neurological deficit after recovery were excluded. Paralysis of the legs within 20 s of intrathecal 2% lignocaine 10 µl confirmed correct catheter position. Two to four hours was then allowed for recovery.

Two pairs of electrodes were placed on the tail and the neck. The minimum electrical current (50 Hz, 1 ms, 0–5 mA) necessary to produce a pain reaction was measured every 5 min. After six readings an i.p. injection of saline (five rats) or RO 15–1788 (five rats) was given in a randomized blind fashion. The current threshold for pain was measured every 5 min for 30 min before and after the intrathecal injection of midazolam 10 µl. Catheter position was then confirmed as before.

The current threshold for pain is plotted for the neck and tail for two rats who received i.p. physiological saline (S) (fig. 1A) or RO 15–1788 (RO) (fig. 1B). The results shown here are typical and are supported by statistical analysis of the grouped data: intrathecal midazolam (M) caused a significant ($P < 0.02$) increase in the threshold for pain in the tail but not in the neck; this response was blocked by RO 15–1788.

In conclusion, intrathecal midazolam causes spinally-mediated analgesia by binding to benzodiazepine receptors in the spinal cord.

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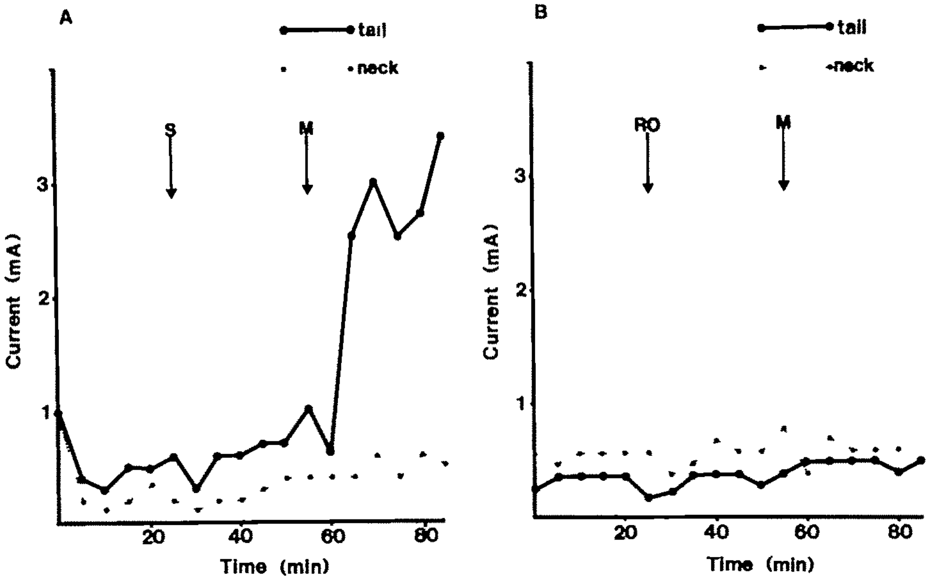

FIG. 1. Current threshold for pain in two rats receiving physiological saline (A) or RO 15-1788 (B). S = saline; M = midazolam; RO = 15-1788.

PCA AND A SPEECH-SYNTHESIZER

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A study was undertaken to compare voice or buzzer tones to provide feedback for patients using patient-controlled analgesia (PCA).

For 2 years we have used a PCA system based on an Apple II microcomputer, a computer-controlled IMED 929 infusion pump and a push button (Gillies, Kenny and McArdle, 1986). The apparatus is programmed to emit various tones with each demand for analgesia. Although, with perioperative assistance, patients did learn how to use the system, some had difficulty understanding the various tones, especially in the first few hours after surgery.

Hull and Sibbald (1981) described a PCA system incorporating a tape-loop, but this proved unreliable for routine use (Harmer, Rosen and Vickers, 1984).

We linked a Digitalker speech synthesizer into our PCA apparatus to provide verbal feedback to indicate operation of the system.

Twenty-six patients were allocated randomly to two groups and studied for the 4 h following surgery. Patients in group I received vocal feedback in the first 2 h and buzzer tone feedback in the second 2 h. Group II patients received buzzer tone feedback during the first period and vocal feedback in the second.

Two patients were withdrawn from the study: one required re-operation and one required no analgesia during the study period.

Results are shown in table II.

TABLE II. *Patient preference for buzzer or vocal feedback*

	Preference			
	Speech	Buzzer	None	No memory
Group I ($n = 13$)	5	1	2	4
Group II ($n = 13$)	10	0	1	1

This study showed that patients preferred vocal feedback and, although four patients in Group I (vocal feedback first) did not remember hearing the voice, the nursing staff reported that three of these patients responded to it more appropriately than to the buzzer tones.

The digitalker speech synthesizer is reliable, simple, easily interfaced to our established PCA system, and provides a more acceptable method of feedback for PCA compared with standard buzzer tones.

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A PROPOSAL FOR ADDITIONAL BLOOD-GAS VARIABLES FOR THE RATIONAL CONTROL OF OXYGEN THERAPY

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With modern oximeters it is possible to obtain fast, accurate measurements of haemoglobin concentration and oxygen saturation as well as of oxygen tension. Therefore, given the general equation (Thomas, 1972) of the oxyhaemoglobin dissociation curve (ODC), it is possible (with some reservations) to locate the curve in a particular patient from a single blood sample. Other blood-gas variables can then be computed, and it is proposed that the following be routinely reported by the blood-gas laboratory:

(1) The % shift from normal of the ODC;
(2) P_{95}—the Po_2 at which the haemoglobin is 95% saturated;
(3) $(Ca_{O_2} - Cx_{O_2})$—the arterio-venous difference in oxygen content for three hypothetical values (x) of the $P\bar{v}_{O_2}$; 5.3 kPa (normal); 2.7 kPa (about the lowest possible (Bryan-Brown et al., 1973)); and 4.0 kPa (midway between the two, and slightly above the value (Kasnitz et al., 1976) which leads to an increase in blood lactate concentration).

Thus, if the objective is to maintain near-maximum oxygen delivery in arterial blood, it is appropriate to aim for a Pa_{O_2} somewhat greater than the P_{95}, whatever the location of the ODC. Current teaching, to aim for a Pa_{O_2} of 70 mm Hg (9.3 kPa), is appropriate for a normal ODC, but will produce only 87% saturation with a curve which is shifted 30% to the right.

However, if $Pa_{O_2} > P_{95}$ can be achieved only at the expense of intensive oxygen therapy, which may damage the lungs, the $(Ca_{O_2} - Cx_{O_2})$ may indicate that this is unnecessary. Thus, in a normal subject, $(Ca_{O_2} - C\bar{v}_{O_2})$ is about 5 ml dl^{-1}; if this value is adjusted for any estimated abnormality in a particular patient and compared with the three $(Ca_{O_2} - Cx_{O_2})$, the likely $P\bar{v}_{O_2}$ in that patient can be estimated by interpolation. If this is greater than 4 kPa it may seem unnecessary to intensify the oxygen therapy, despite a $Pa_{O_2} < P_{95}$.

Conversely, even with $Pa_{O_2} > P_{95}$, especially with a lef-shifted curve and a low haemoglobin concentration, the estimated $P\bar{v}_{O_2}$ may be low, suggesting the need for increasing the haemoglonin concentration or shifting the ODC to the right, which usually improves oxygen availability to the tissues.

Initial tests suggest that the accuracy of the Ciba–Corning "Co-oximeter" M2500 is sufficient to estimate P_{95} to within 5% and $(Ca_{O_2} - Cx_{O_2})$ to within 10% for measured saturations up to 94%.

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ANTERIOR AND LATERAL APPROACHES TO THE SCIATIC NERVE: A STUDY USING COMPUTERIZED TOMOGRAPHY

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Computerized tomography was used to study the anatomical basis of the anterior and lateral approaches to the sciatic nerve (Ichiyanagi, 1959; Beck, 1963; Guardini, Waldron and Wallace, 1985). Patients undergoing CT scans of the pelvis gave permission for the surface land-marks for each approach to be marked on the skin.

Subsequent analysis of the tomographic cuts through the thigh at the points described by the original authors revealed that a substantial failure rate can be expected with the anterior approach. It is evident that in 14 of 34 subjects (41%) this approach would be impossible to perform as the nerve would be behind the femur.

The lateral approach is likely to yield a higher success rate utilizing either published technique. Using the clearer landmarks offered by Guardini, Waldron and Wallace (1985) it can be shown that only four of 34 blocks (12%) would be impossible to perform for the same reason. In addition, the sciatic nerve was within 8 cm of the skin surface in seven of 34 subjects (21%). This is more superficial than previously described and may represent an additional reason for difficulty with this approach.

Computerized tomography shows that the sciatic nerve in the upper thigh has an almost constant relationship with the ischium. This suggests that the anterior approach will be more successful if the needle insertion is made medial to the femoral neurovascular bundle and the needle "walked" laterally off the ischium. The highest success rate should be achieved with the lateral approach and by adopting a more posterior point of needle insertion.

The suggested modifications have been used in clinical anaesthetic practice. Twenty-six of 30 blocks (87%) were successful using the anteromedial approach. Fourteen of 16 blocks (87%) were successful using the posterolateral approach.

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EXTRADURAL PRESSURE DURING LABOUR

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Galbert and Marx (1974) showed an increase in extradural pressure which was proportional to the dilatation of the cervix and suggested a progressive engorgement of extradural veins during labour. Marx, Zemaitis and Orkin (1961) found no changes in cerebrospinal fluid (CSF) pressure during advancing labour in painfree patients. Since the extradural pressure is also influenced by the CSF pressure (Shah, 1981), we investigated the extradural pressure during labour in painfree patients.

Informed consent for the investigation was obtained from 10 patients who requested extradural analgesia in early labour. The extradural pressure was measured with the patients in the left lateral position, using the catheter as a manometer. Each patient was visited approximately 2-hourly and their extradural pressure recorded. The dilatation of the cervix was extrapolated from the patient's partogram and recorded with each pressure measurement. A value of 2 cm H_2O was deducted from the extradural pressure recordings to allow for the capillarity effect.

The mean extradural pressure during early labour was 14.7 cm H_2O. There was no significant variation in extradural pressure in any patient during their advancing labour (fig. 2).

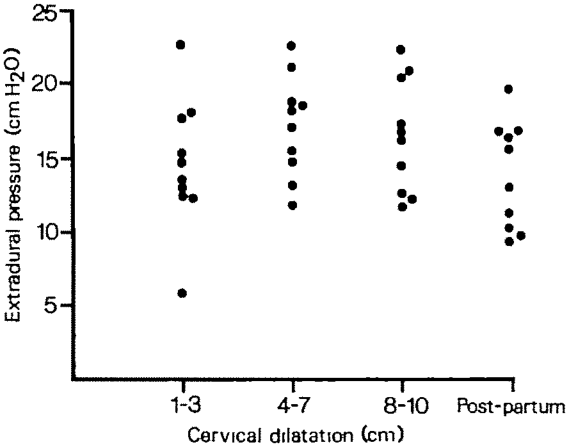

FIG. 2. Extradural pressure in 10 women in labour.

During labour the CSF pressure increases as a result of straining and movement of the patient. The increase is proportional to the intensity of discomfort experienced by the patient, and thus with the advance of labour. The reported increase in extradural pressure associated with cervical dilatation may be mediated through the increase in CSF pressure and not by progressive engorgement of the extradural veins as suggested. Advancing labour does not produce significant changes in extradural pressure when labour is painfree.

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DIFFERENTIAL NERVE BLOCKADE: ESTERS *V.* AMIDES

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Structurally, all the commonly used local anaesthetic drugs comprise an aromatic ring structure joined to an amine group by a chain containing either an ester or an amide linkage. A previous study (Wildsmith et al., 1985) showed that the lipid solubility of a series of ester-linked compounds affected the relative rate at which different types of peripheral nerve fibre were blocked, as well as the absolute potency of the agents.

The present study was designed to establish whether the same was true of a series of amide-linked agents, and to allow comparison of the two groups of drugs. The same *in vitro* desheathed rabbit vagus nerve preparation was used under exactly the same conditions as in the previous study. Submaximally blocking concentrations of etidocaine, lignocaine and W36017 (the dimethyl analogue of lignocaine) were applied to nerves until stable blockade had developed. On the basis of changes in the heights of the compound action potentials for A, B and C fibres, dose–response curves were constructed and also plots of the rate of development of blockade.

The results again confirmed that A fibres are the most sensitive to blockade by local anaesthetic and C fibres the least. As with the ester drugs, equipotent concentrations of the amides blocked C fibres at approximately the same rate, but the absolute and relative rate of development of A fibre blockade was related to lipid solubility. As the latter increased, so did the rate of A fibre blockade, so that with etidocaine, A fibres were clearly blocked faster than C.

Taking the results of the two studies together suggests that an agent with a high pKa and low lipid solubility might be used to produce a differential C fibre blockade. Further, using calculated lipid solubility of the base form of the drug (C'LOG P) as a basis for comparison, it would seem that the ester structure has an inherently more potent action than the amide. This may relate to the molecular "bulkiness" of the latter grouping restricting access to the drug receptor.

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EFFECT OF DOSE, VOLUME AND CONCENTRATION OF BUPIVACAINE INJECTION ON EXTRADURAL BLOCKADE

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Many texts suggest that the factors affecting the spread of an extradural injection are clearly defined, but both clinical experience and the evidence of clinical studies that have been performed (Grundy et al., 1978; Park et al., 1982) do not support these views. In fact, there are few randomized controlled trials in the literature and it is felt that such studies are needed.

Thirty patients, aged 20–50 yr, undergoing extradural anaesthesia for varicose vein surgery were entered in a randomized double-blind study. The extradural technique was standardized and the patient allocated to one of three groups ($n = 10$): group 1: 0.75% bupivacaine 10 ml (75 mg); group 2: 0.5% bupivacaine 15 ml (75 mg); group 3: 0.75% bupivacaine 15 ml (112.5 mg).

The onset of sensory (analgesia to pinprick) and motor blockade (Bromage score), pulse and arterial pressure were recorded at 5-min intervals for 30 min after injection. Regression of sensory and motor blockade were assessed hourly until complete.

Conditions were adequate for surgery in every patient. The mean upper level of sensory blockade was virtually the same in each group (table III). There was no significant difference in the block achieved with bupivacaine 75 mg when administered in either 10 ml or 15 ml of solution. However, compared with both 10 ml of 0.75% and 15 ml of 0.5%, 15 ml of 0.75% bupivacaine resulted in more rapid onset and longer duration of sensory analgesia, with a greater degree of motor block (table III). Circulatory changes were minimal and no patient required treatment for hypotension. In this study there was no significant correlation between cephalad spread of the block and patient age, weight, height and body mass index.

TABLE III. *Extradural blockade in patients receiving bupivacaine. Comparing group 3 with groups 1 and 2:* *$P < 0.05$ *Bonferroni t test;* †$P < 0.05$ *Chi squared with Bonferroni correction*

	Group 1 (10 ml of 0.75%)	Group 2 (15 ml of 0.5%)	Group 3 (15 ml of 0.75%)
Maximum spread	T9.7	T8.9	T9.2
(mean dermatome (SEM)	(0.45)	(0.9)	(0.7)
Onset to T12 (min)	14.5	17	9.5*
(mean (SEM))	(1.5)	(0.8)	(1.1)
Duration	5.3	4.95	6.6*
(mean (SEM))	(0.35)	(0.36)	(0.36)
Bromage score 2 or more (No. patients)	1	1	5†

We conclude that, under these conditions, volume and dose have little effect on extradural spread. The duration of sensory analgesia and degree of motor block were related to drug dose and not concentration of solution.

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PRESSURE REVERSAL OF SEDATION PRODUCED BY BENZODIAZEPINES?

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Anaesthesia produced by gaseous and i.v anaesthetics and by benzodiazepines has been reported to be "reversed" by a hyperbaric environment (Halsey, Wardley-Smith and Green, 1978; Cohen, Halsey and Wardley-Smith, 1984). However, the effects of pressure upon sedation have not been examined.

Using a pair of activity wheels, in a pressure chamber, sedation was measured in terms of decrease in locomotor activity. Two female TO mice, one injected i.p. with benzodiazepine and the other injected i.p. with the drug vehicle, were each enclosed in a separate wheel of the apparatus. The chamber was maintained at 1.3 atmospheres absolute (ATA) or pressurized to 51 ATA; the $Po_2 = 0.4$–0.5 ATA in all experiments. The pressure of 51 ATA was considered the maximum possible without neurological signs associated with high pressure.

Benzodiazepines examined were diazepam 10 mg kg^{-1} and 20 mg kg^{-1}, midazolam 10 mg kg^{-1} and chlordiazepoxide hydrochloride 10 mg kg^{-1}. The control animals for the midazolam studies received saline i.p.; all the other control animals received Tween 80/saline. All the benzodiazepines were found to decrease activity. However, it should be noted that, if disturbed, the treated mice were able to move apparently normally and were therefore considered to be no more than sedated.

Measurements of activity, in arbitrary units, were started 20 min after injection and maintained for 60 min. The data for both the control and treated animals were determined at 1 and at 51 ATA. Results, presented in table IV, show that, for all benzodiazepines tested, the decrease in the levels of activity were similar at the two pressures.

TABLE IV. *Percentage of control activity (SEM)*

	1 ATA	51 ATA	*n*
Diazepam 10 mg kg^{-1}	84.6 (7.7)	69.1 (7.0)	9
20 mg kg^{-1}	35.5 (5.3)	52.6 (6.7)	6
Midazolam 10 mg kg^{-1}	36.8 (5.8)	32.6 (5.6)	5
Chlordiazepoxide 10 mg kg^{-1}	24.5 (4.6)	43.9 (6.3)	6

From these data it can be inferred that there are no major differences in benzodiazepine sedation at 1 and 51 ATA.

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DANTROLENE REDUCES SUXAMETHONIUM-INDUCED MYALGIA, MYOGLOBIN AND CREATININE KINASE CHANGES

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Oral dantrolene administration has been found to reduce suxamethonium-induced myalgia (Collier, 1979) and increase myoglobin concentration (Laurence, 1985). Previous work has also shown that, of pretreatments studied, only pretreatment with non-depolarizing drugs was effective in preventing increases in myoglobin and 24-h creatinine kinase (CK) concentrations and reducing myalgia following intermittent suxamethonium administration in laparoscopy patients (Laurence, 1986).

We have studied the effectiveness of oral dantrolene to prevent myalgia and biochemical changes following intermittent administration of suxamethonium. A gynaecological population identical to that in our previous study was used.

Patients presenting for gynaecological laparoscopy gave signed, informed consent and were allocated randomly to control or treatment groups. All patients were given an oral premedication and those in the treatment group were additionally prescribed oral dantrolene 1.5 mg kg^{-1} 2–4 h before operation.

A preinduction blood sample was drawn from an indwelling venous cannula for measurement of serum myoglobin and CK. As in previous studies, thiopentone plus suxamethonium was used for induction, followed by intermittent suxamethonium and mechanical ventilation of the lungs with nitrous oxide and 0.5% enflurane. Further blood samples were drawn at 5, 10 and 20 min after first suxamethonium administration.

All patients were visited the next morning. They were assessed in an initially non-leading manner and scored for myalgia. A final blood sample was drawn. All specimens were frozen before assay in batches for myoglobin, by radioimmunoassay, and CK.

Forty patients (20 control, 20 treatment) completed the study. Mean age and weight were similar for control and treatment groups. Preinduction myoglobin and CK concentrations were similar in both groups. Following suxamethonium administration in the control group, there was an immediate increase in serum myoglobin concentration in 15 out of 20 patients, increasing by a mean of 161 μg litre^{-1} at 20 min ($P < 0.0001$; *t* test, compared with values before induction). There were no increases in CK concentration during the operation. The 24-h myoglobin concentration was 11 μg litre^{-1} greater than preinduction values, but CK concentrations increased by 173 i.u. Total myalgia score for the group was 52 (maximum score 100).

In the treatment group, there was a small increase in serum myoglobin in three of 20 patients, increasing by a mean of 33 μg litre^{-1} for the whole group at 20 min. This was significant ($P < 0.001$) compared with the preinduction values. Mean increase in myoglobin concentration at 24 h was 4.5 μg litre^{-1}, that for CK was 10 i.u. Total myalgia score was 23 for the group, which was significantly less than the control group ($P < 0.01$; Mann–Whitney).

We conclude that oral dantrolene pretreatment obtunds suxamethonium-induced myoglobin and CK concentration changes and significantly reduces postoperative myalgia. Nausea and vomiting were seen in two of 20 patients given dantrolene

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POST-TETANIC POTENTIATION AT THE RAT NEUROMUSCULAR JUNCTION PARTIALLY BLOCKED BY ATRACURIUM

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Post-tetanic potentiation (PTP) is a long-lasting increase in responsiveness which follows a period of repetitive stimulation Thus after a tetanus, a single test pulse produces a larger twitch

TABLE V. *Effect of atracurium on twitch, tetanic post-tetanic twitch tensions and on the post-tetanic potentiation at the rat neuromuscular junction. Mean values ± SEM*

	Twitch (A) (0.2 Hz) (g)	Tetanus (20 Hz) (g)	PTT (B) (0.2 Hz) (g)	PTP $(B-A)/A$ × 100 (%)
Control	2.4 ± 0.2	4.5 ± 0.2	3.0 ± 0.1	25 ± 1
Atracurium	1.1 ± 0.1	1.5 ± 0.1	1.6 ± 0.2	45 ± 2
Change	54 ± 2%	67 ± 3%	47 ± 1%	—

tension than before the tetanus. The presence of PTP, which is mainly caused by increased transmitter release, has been demonstrated in both man and animal species, in the presence and absence of neuromuscular blocking agents (Hutter, 1952; Standaert, 1964; Gissen and Katz, 1969).

In the present investigation, we have studied, in rat isolated hemidiaphragm preparation: (a) the phenomenon of PTP in the presence and absence of atracurium, and (b) the influence of PTP in the restoration of neuromuscular transmission partially blocked by atracurium.

The phrenic nerve was stimulated at 0.2–100 Hz with 5–10 V (maximal) and 0.2-ms pulse duration. The twitch, tetanic and post-tetanic twitch responses were recorded isometrically. The post-tetanic twitch response (PTT) was elicited 5 s after a tetanic stimulation at 20 Hz for 30 s duration. The PTP value was measured as a percentage difference between the height of the twitch response immediately after and before the tetanus. With this procedure, a PTP value of 25% was obtained in the absence of atracurium.

Atracurium 0.1–10 μmol litre^{-1} reduced the twitch, tetanic and post-tetanic twitch tensions (table V). The mean IC$_{50}$ values (concentration to produce 50% maximum inhibition) of atracurium-induced inhibition of indirect twitch tension was 0.8 ± 0.1 μmol litre^{-1} (mean ± SEM; $n = 8$). Furthermore, in the presence of atracurium 0.8 μmol litre^{-1}, a PTP value of 45 ± 2% was obtained, indicating a significant potentiation of neuromuscular transmission partially blocked by atracurium. Since atracurium also reduced the PTT response (table V), it is possible that it may have a presynaptic inhibitory action at the rat neuromuscular junction.

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INTERACTION OF TRIMETAPHAN WITH DIFFERENT NONDEPOLARIZING NEUROMUSCULAR BLOCKERS AT THE NEUROMUSCULAR JUNCTION

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The neuromuscular junction contains more than one subtype of acetylcholine receptor and each nondepolarizing neuromuscular blocking agent is regarded as having its own individual spectrum of actions on this system. The postjunctional membrane carries the classic nicotinic neuromuscular receptors, while those receptors situated prejunctionally may have a greater similarity to those in autonomic ganglia (Bowman, 1980). This study was undertaken to investigate the interaction of a ganglionic blocking agent with different non-depolarizing neuromuscular blocking agents.

The rat phrenic nerve–hemidiaphragm preparation was used, suspended in Krebs solution at 37 °C, aerated with 5% carbon dioxide in oxygen. Isometric contractions evoked by 0.2-ms supramaximal square wave stimuli at 0.1 Hz to the phrenic nerve were recorded on a Grass polygraph. Cumulative

TABLE VI. *Results (mean ± SD). When compared with slope in absence of trimetaphan:* *P < *0.05;* **P < *0.01*

	Trimetaphan concentration (mol litre^{-1})			
	0	3.35×10^{-5}	1.00×10^{-4}	1.67×10^{-4}
Pancuronium				
Slope	277 ± 25	189 ± 30**	158 ± 29**	215 ± 65*
EC$_{50}$	2.62 ± 0.35	2.19 ± 0.52	1.86 ± 0.2	1.32 ± 0.23
EC$_{50}$ ratio	—	0.83	0.71	0.50
Tubocurarine				
Slope	262 ± 62	184 ± 11**	177 ± 29**	163 ± 19**
EC$_{50}$	0.91 ± 0.07	0.66 ± 0.06	0.43 ± 0.06	0.26 ± 0.05
EC$_{50}$ ratio	—	0.72	0.47	0.28
Metocurine				
Slope	135 ± 30	170 ± 55	190 ± 50*	160 ± 18
EC$_{50}$	2.9 ± 0.35	2.05 ± 0.33	1.37 ± 0.16	0.80 ± 0.16
EC$_{50}$ ratio	—	0.69	0.46	0.27

concentration–response relationships were constructed for each of three neuromuscular blockers (tubocurarine, metocurine and pancuronium) alone and in the presence of the ganglion blocking agent trimetaphan. Each concentration–response relationship was constructed using a minimum of three points between 15% and 85% twitch inhibition. Six different preparations were used for each combination. The slopes and EC_{50} (concentration to produce 50% twitch inhibition) were recorded in each case and the EC_{50} ratios calculated as (EC_{50} with trimetaphan/EC_{50} without trimetaphan). The EC_{50} ratios were then used as a means of quantifying the shift of the log concentration–response relationship.

The results are displayed in table VI. The EC_{50} ratios for tubocurarine and metocurine agree closely, indicating that both are potentiated by trimetaphan to a similar degree in a dose dependent manner. The EC_{50} ratios for pancuronium however are quite different, showing that pancuronium is potentiated dose-dependently by trimetephan to a much lesser degree than either of the other two agents. The results of this study thus reinforce previous evidence that the mechanism of action of pancuronium on the neuromuscular junction differs from that of tubocurarine and metocurine, whilst these latter two agents have a very similar action.

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THE "PRIMING PRINCIPLE": GALLAMINE AND ATRACURIUM COMPARED

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A small "priming" dose of atracurium administered before a subsequent dose of atracurium has been recommended to facilitate endotracheal intubation (Nagashima et al., 1984). Since bradycardia and hypotension have been reported with atracurium (Carter, 1983), we investigated the use of a subclinical dose of gallamine or atracurium injected 3 min before atracurium 350 µg kg^{-1} and compared the intubating conditions, duration of neuromuscular blockade and cardiovascular effects.

With Ethical Committee approval, we studied 16 adult patients of either sex (ASA I and II) undergoing minor surgical procedures. The patients were randomly allocated to two groups to receive either gallamine 0.6 mg kg^{-1} or atracurium 0.075 mg kg^{-1}. After receiving temazepam 0.3 mg kg^{-1} orally 1–2 h before operation, anaesthesia was induced with fentanyl 1 µg kg^{-1} followed by thiopentone 4 mg kg and maintained with 50% nitrous oxide in oxygen and 0.5% halothane. The ECG was monitored throughout and the arterial pressure recorded every 3 min. Evoked integrated compound action potentials of the hypothenar muscles were recorded when the ulnar nerve was supramaximally stimulated with square wave pulses, pulse width 100 µs every 20 s at the wrist using surface electrodes. A TOF pattern of stimulation was used and single twitch depression (T1/TC) and TOF (T4/T1) were recorded. Intubation was attempted 90 s after the bolus injection of atracurium 350 µg kg^{-1}. Ease of intubation was scored (IS): 1 = excellent, 2 = slight cough, 3 = moderate cough and bucking and 4 = impossible. The patients were ventilated to an end-tidal carbon dioxide concentration of 5%. Onset time, that is time to 95% depression of twitch height (T1/TC 5%), offset time (T1/TC 25%) and ease of reversal (time to T4/T1 50%) were measured and the results analysed using the Wilcoxon's Rank Sum test. The results are expressed as means and standard deviations (table VII).

TABLE VII. *Effects of priming doses of atracurium or gallamine.* *$P < 0.05$

	Gallamine/ atracurium	Atracurium/ atracurium
IS	1.3 (0.5)	1.4 (0.7)
Priming dose (mg)	37.3 (8.0)	5.4 (0.9)
T1/TC 5% (s)	125.0 (63)	123.8 (60.9)
T1/TC 25% (min)	38.6 (7.7)	44.8 (11.1)
T4/T1 50% (s)	79.1 (30.31)	116.8 (78.9)
Slowest HR (beat min^{-1})	90.1 (28.6)	51.9 (3.9)*

This study shows that a subclinical dose of gallamine before atracurium significantly increased the heart rate compared with atracurium in divided dose ($P < 0.05$). Satisfactory intubating conditions were obtained in each group at 90 s. There were no significant differences in systolic arterial pressure, onset or recovery of neuromuscular blockade.

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INDUCED HYPOTENSION AS A MEASURE OF OPIATE REQUIREMENT

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In a technique of anaesthesia for major surgery using thiopentone, nitrous oxide, an opiate, alcuronium and trimetaphan, the maximum dose of trimetaphan has been limited to 20 mg in each 5 min (bolus doses). At this dose limit, hypotension within the range 60–80 mm Hg systolic is achieved at an opiate dose which is characteristic for the individual patient. This varies greatly: in the series reported here, from 1 to 16 mg of phenoperidine (895 patients), and from 10 to 100 mg of papaveretum (102 patients). The mechanism appears to be suppression of the cardiovascular reflex response to surgery.

The end-point marked by the appropriate opiate dose is close to that at which reversal of excessive respiratory depression is required at the end of anaesthesia to allow a respiratory rate of 10 b.p.m. or more. This is achieved when necessary by increments of naloxone 80 µg.

Adjusted to proportion, the distributions of patient numbers become:

Phenoperidine	39	410	200	126	20	53	34
Papaveretum	35	451	203	132	9	27	27

TABLE VIII. *Opiate requirement as judged by induced hypotension of 60–80 mm Hg systolic, and requirement for naloxone to achieve a respiratory rate of at least 10 b.p.m.*

Phenoperidine (mg)	1	2	3	4	5	6	7	8	(7 over 8 mg)
No. of patients	39	410	200	126	20	53	3	34	(Total 895)
% Given naloxone	7.7	41	61	57	45	53	0	56	
Naloxone (μg mg^{-1})	6.2	16.5	16.1	17.3	12.8	11.1	0	10.3	
Papaveretum (mg)	10	20	30	40	50	60	80	100	
No. of patients	4	51	23	15	1	3	3	2	(Total 102)
% Given naloxone	0	19.6	39.1	33.3	0	33.3	33.3	0	
Naloxone (μg/10 mg)	0	8.6	9.2	9.3	0	13.3	6.7	0	

A Chi-squared goodness of fit test on the first four classes shows good agreement ($P < 0.05$). Fit is less good for the others, but numbers for papaveretum are too small.

In the phenoperidine group, 17 patients (2%) were judged to be resistant to trimetaphan resulting in excessive phenoperidine dosage, and a naloxone requirement of 240 μg or more. This group contained eight patients with a diagnosis of hypertension, compared with 82 in the whole group. This is a significant difference (Chi squared test, $P < 0.0001$). The mean age of this group (64 yr) is not significantly different from that of the whole group (61 yr) (normal distribution test, $P < 0.1$). No such resistant group could be identified in the patients given papaveretum, suggesting that this drug provides superior suppression. However, five patients given papaveretum required a further postoperative increment of naloxone compared with one phenoperidine patient (Chi-squared test, $P < 0.0001$). Total dose of naloxone in the phenoperidine group was 39.8 g and in the papaveretum group 2.6 g (Chi-squared test, $P < 0.01$). Comparing the mean doses for the two groups, phenoperidine 1 mg is equivalent to papaveretum 9.6 mg.

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DISPOSITION OF NALBUPHINE DURING ANAESTHESIA

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Nalbuphine is a semi-synthetic opioid partial agonist of the morphinan series. To date, there are only limited kinetic data on the peri-operative use of the drug during balanced anaesthesia (Lake et al., 1982).

Ten patients (two male) aged 24–61 yr, weights 53–81 kg, ASA I or II, were studied while undergoing lower abdominal or body surface surgery. After premedication with diazepam 10 mg, anaesthesia was induced using thiopentone 4 mg kg^{-1}, and maintained with 67% nitrous oxide in oxygen supplemented with halothane ($\leqslant 0.5\%$). Controlled ventilation was carried out after neuromuscular blockade following alcuronium 0.25 mg kg^{-1}. Venous blood samples were collected for up to 9 or 10 h after a dose of nalbuphine 20 mg i.v., and plasma drug concentrations measured by HPLC with electrochemical detection. The sensitivity of the method was 0.1 ng ml^{-1} and the coefficient of variation 1–4% over the concentration range measured (Keegan and Kay, 1984).

Anaesthesia was uneventful in nine patients, the other patient suffering a profound bradycardia (38 beat min^{-1}) following injection of the nalbuphine.

Plasma drug concentrations declined in a curvilinear manner, and varied between 30 and 62 ng ml^{-1} at extubation. Kinetic parameters were calculated using a model-independent approach (Benet and Galeazzi, 1979). The mean terminal half-life was 135.5 min (SD 55.4); volume of distribution at steady state (V^{ss}) 159.9 litre (39.6); V^{β}_{1} 207.1 litre (71.2); and clearance 1095 ml min (277). The mean residence time was 149.7 min (40.4).

Animal studies suggest that nalbuphine undergoes negligible extrahepatic metabolism; thus its clearance in man will be sensitive to those factors affecting hepatic blood flow.

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DOSE-RESPONSE STUDY WITH NALBUPHINE HYDROCHLORIDE FOR PAIN AFTER UPPER ABDOMINAL SURGERY

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Nalbuphine hydrochloride may reach a ceiling for analgesia (Kay, 1983; Eisele and Steffey, 1984) and following high doses, analgesia could possibly be reversed (Gal, DiFazio and Moscicki, 1982). The present study aimed to assess analgesia and sedation with progressively increasing plasma concentrations of nalbuphine in patients following upper abdominal surgery.

Six male patients were studied the morning after surgery for highly selective vagotomy. During surgery, nalbuphine 20 mg was administered for analgesia and continued as a constant i.v. infusion (2 mg kg^{-1}/24 h) up to the time of the study. Each patient could be given additional doses of nalbuphine 10 mg i.m. every 2 h for pain. At 06.00 h the nalbuphine infusion was discontinued and 1 h later the experimental nalbuphine i.v. infusion was started at 1 mg kg^{-1}/24 h. The infusion rate was doubled at 1-h intervals over 3 h with a loading dose given i.v. at the start of the 2nd, 3rd and 4th hours (mean total dose 61.8 ± 9.2 mg in 4 h). The infusion regimen was designed to obtain increasing nalbuphine plasma concentrations that were relatively steady by the end of each hour. Venous blood samples (10 ml) were taken 15 min apart, at the end of each hour, in order to assess how well steady state plasma concentrations had been achieved. Pain and sedation were assessed by patients (LAS) and a single observer at 1-h intervals.

The nalbuphine plasma concentration profiles for each patient were similar. The mean concentrations were almost steady: 72.5–67.9, 71.1–82.4, 115.1–112.7, 200.9–207.7 mg ml^{-1} in the last 15 min at the end of the 1st, 2nd, 3rd and 4th hours, respectively. The objective and subjective pain and sedation scores did not change significantly despite the large increase in plasma concentration. However, the mean LAS for pain increased when the plasma concentrations were greater, suggesting that the nalbuphine analgesia had been reversed. Marked sedation was present throughout the study which may have influenced the assessments. No serious side-effects were observed.

The expression E'max (Effect maximum) is proposed to replace the term "ceiling effect". The mean E'max for nalbuphine efficacy (E'e max) in this study appeared to represent a plasma concentration between 70 and 115 ng ml^{-1}.

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COMPARISON OF BUPRENORPHINE AND NALBUPHINE FOR PAIN IN PATIENTS FOLLOWING ABDOMINAL SURGERY

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Nalbuphine hydrochloride is an effective analgesic in some patients (Bahar, Rosen and Vickers, 1985) but not in others (Kay, 1983). This double-blind, sex-stratified study compared the effects of buprenorphine 0.15 mg ml^{-1} and nalbuphine 10 mg ml^{-1} in patients following elective abdominal surgery. The trial drugs were prepared by Pharmacy.

Fifty-five patients between the ages of 20 and 65 yr, ASA I or II, were randomly allocated to two groups, one receiving buprenorphine, the other nalbuphine. Trial drug (0.5–3 ml) was given i.v. during surgery and continued as an i.v. infusion (0.2 ml kg^{-1}/24 h) for 20 h after surgery. In recovery, patients received i.v. infusions of trial drug 1 ml/5 min until analgesia was achieved. Each patient could be given additional trial drug 1 ml i.m. every 2 h for pain.

Assessments of pain and sedation were made at 1, 3, 6 and 20 h after surgery by patients (LAS) and one observer. Arterial blood-gas tensions were estimated the day before and repeated at 20 h after surgery for comparison. The physiotherapist assessed patients before and 20 h after surgery for: mobility, chest expansion, ability to cough, level of pain and performance.

The two groups of patients (buprenorphine $n = 26$ and nalbuphine $n = 29$) were equally matched for age and physical characteristics. Nine patients had to be withdrawn from the study (mean 2.5 h after survery) because of inadequate analgesia. The trial set out to study 100 patients. However, all the withdrawn patients had received nalbuphine ($P < 0.006$), so the study had to be discontinued before completion. When the patients unable to mark the LAS, because of severe pain, were included, the pain scores were significantly higher at each assessment in the nalbuphine group. Sedation scores were similar in both treatment groups. Patients in the nalbuphine group requested significantly greater additional analgesia ($P < 0.0002$). The mean respiratory rate was significantly slower in the buprenorphine group ($P < 0.0001$) with a significantly greater increase from the pre- to the post-operative $P\mathrm{co}_2$ value ($P < 0.0001$). The physiotherapy assessments showed significantly greater pain relief ($P < 0.02$) and greater chest expansion ($P < 0.03$) in the buprenorphine group at 20 h.

The results show that nalbuphine is a less effective analgesic than buprenorphine in patients with severe pain following abdominal surgery.

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PALMAR SWEAT AND HEART RATE CHANGES DURING STRESS RESPONSE ATTENTUATION WITH ALFENTANIL

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We are currently investigating the production of palmar sweat during anaesthesia and surgery and its correlation with cardiovascular variables as an index of stress (Bishop, 1983). In one of a series of studies the palmar sweat and heart rate changes were recorded during an attempt to attenuate the stress response to laryngoscopy and intubation by pretreatment with alfentanil.

Two groups of patients were studied. Group 1 consisted of 20 patients given alfentanil 30 µg kg^{-1} 1 min before induction and intubation. To ensure that the results obtained were in response to events and not to time, a delay was introduced to the intubation procedure of the patients in group 2 After base-line measurements were taken, values were recorded at specific events such as induction, laryngoscopy and intubation.

In group 1 the mean palmar sweat response remained above control values throughout the study, while the mean heart rate decreased significantly during laryngeal spraying.

In group 2 we were forced to abandon the study because two patients out of six suffered sinus arrest at the onset of laryngeal spraying and a third developed a severe bradycardia.

We suggest that alfentanil 30 μg kg^{-1} as pretreatment may attenuate or completely abolish the tachycardia associated with the sympathetic response and allow unopposed vagal activity to produce bradycardia or sinus arrest. In this study this effect was more pronounced in the group of patients in whom intubation was delayed.

The increase in palmar sweat production after induction of anaesthesia and its sustained increase during intubation suggest that heart rate may not be as good a measure of stress as has hitherto been assumed, and that pharmacological damping of the cardiovascular system may not necessarily indicate an ablation of the stress response to laryngeal stimulation.

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POSTER PRESENTATIONS

RECOVERY FROM OUTPATIENT ANAESTHESIA: COMPARISON OF PROPOFOL AND ISOFLURANE MAINTENANCE

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We have previously demonstrated that a propofol induction with isoflurane maintenance provides good anaesthesia with a rapid and complete recovery (O'Toole et al., 1986). The present study compares the recovery characteristics of 60 healthy unpremedicated patients, 16–55 yr, 45–80 kg, undergoing minor gynaecological surgery, who were randomly allocated to one of two equal groups. Anaesthesia was induced with propofol 2.5 mg kg^{-1} over 20 s and maintained with 66% nitrous oxide in oxygen plus either incremental doses of propofol (group PP) or isoflurane (group PI). Isoflurane maintenance was initially with 3%, reducing to 1–1.5% thereafter. Propofol maintenance was with 10-mg increments as required. A second anaesthetist, unaware of the maintenance technique used, assessed recovery using both clinical criteria and psychomotor testing. Initial clinical recovery consisted of time to eye opening, giving correct date of birth (DOB) and orientation in time and place. Other clinical criteria were gait and degree of alertness as assessed at 20, 40 and 60 min after operation. Psychomotor testing, consisting of "four choice reaction times" (CRT) (Wilkinson and Houghton, 1975) and "p-deletions", was carried out at 20, 40 and 60 min after operation and compared with preoperative baseline values. Identical testing was carried out in a non-anaesthetized control group ($n = 30$). Results were statistically analysed using the Mann–Whitney U test, independent t test, analysis of variance, χ^2 and Fisher's exact probability tests. All findings are expressed as mean ± SEM.

All groups were broadly comparable with respect to age and weight. Anaesthesia was significantly ($P < 0.05$) longer for the PI group (12.83±0.99 min) than for PP (9.69±0.62) min, reflecting the longer delay in achieving adequate operating conditions in the PI group The PP group required an average of 7.53±0.71 increments. Initial clinical recovery was more rapid in the PP group using all end points (table IX).

TABLE IX. *Mean ± SEM times (min) to initial clinical recovery for incremental propofol (PP) and propofol–isoflurane (PI).* **$P < 0.01$

	PP	PI
Eye opening**	3.83±0.43	7.32±0.51
Correct DOB**	4.52±0.48	7.70±0.51
Orientation**	4.57±0.46	7.75±0.50

By 20 min the groups were comparable with respect to both clinical and psychomotor testing. Ataxia and sedation, equal in both groups were negligible by 40 min, by which time CRT and p-deletion scores had surpassed baseline values. Some patients in the PP group were euphoric on awakening. Minor postoperative sequelae (headache, nausea) were uncommon in both groups.

Recovery from PI was initially slower, but by 20 min both groups were comparable, using both clinical and psychomotor criteria.

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ABDOMINAL MUSCLE ACTIVITY INCREASES AFTER UPPER ABDOMINAL SURGERY

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The reduction of lung volume that occurs after upper abdominal surgery (UAS) has been attributed, in part, to reflex spasm of the abdominal muscles. Although this has been demonstrated in dogs 1 h after cholecystectomy (Dureuil et al., 1985), no information is available in patients after UAS.

We studied healthy patients undergoing cholecystectomy ($n = 10$) or gastric surgery ($n = 8$). Anaesthesia was standardized. Abdominal muscle activity was measured by simultaneous recordings of the electromyogram (EMG) using surface electrodes, from the following sites: the 9th right intercostal space in the anterior axillary line (lower intercostal); 2 cm below the costal margin in the mid clavicular line (MCL) (external oblique); and 2 cm below the umbilicus in the MCL (internal oblique). The patients were studied standing and lying before operation, and 3 and 24 h after surgery in the supine position. The EMG signal was amplified (band width 20 Hz–2 kHz) (Neurolog NL 104/125) and recorded on FM magnetic tape (Digitimer D146). The signal was subsequently rectified and integrated as an exponential average (NL703) with a time constant of 100 ms and recorded (UV recorder, Bell & Howell 5–137).

The values given (table X) are the integrated EMG averaged over six breaths, expressed as a fraction of the preoperative value in the upright position. There was very little activity in the supine patients before operation. Tonic activity was present, particularly in the lower abdomen, in standing patients. After operation there was a marked increase in lower intercostal and abdominal muscle activity at 3 and 24 h. Most patients showed a progressive increase in EMG activity during expiration with an abrupt decrease at the onset of inspiration. This phasic pattern was observed in 16 patients at the 3-h assessment and 12 patients at the 24-h assessment.

TABLE X. *Integrated EMG (fraction of standing activity before operation) (means ± SD). Comparison with supine value before UAS. Wilcoxon Signed-Rank Test:* *P < 0.02

	Lower intercostal	External oblique	Internal oblique
Before UAS			
Standing	(1.0)	(1.0)	(1.0)
Supine	0.5 ± 0.3	0.7 ± 0.3	0.4 ± 0.3
3 h after UAS			
Expiration	3.3 ± 2.0*	3.5 ± 1.9*	2.5 ± 1.9*
Inspiration	2.1 ± 1.2	2.1 ± 1.6	1.4 ± 1.5
24 h after UAS			
Expiration	3.0 ± 1.7*	3.0 ± 1.2*	2.0 ± 1.3*
Inspiration	2.3 ± 1.2	2.1 ± 1.2	1.2 ± 1.1

This expiratory muscle activity may be responsible for the decrease in FRC after UAS and contribute to the high incidence of pulmonary complications. The activity of these muscles has to be considered in the analysis of chest wall motion and intra-abdominal pressure changes after UAS.

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ACUPUNCTURE ALSO REDUCES THE EMETIC EFFECTS OF PETHIDINE

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Previous studies from this Department have shown that manual needling of P6 acupuncture point (Neiguan) significantly reduced the incidence of preoperative sickness in patients premedicated with meptazinol 100 mg (Chestnutt and Dundee, 1985) and nalbuphine 10 mg (Lynas, Ghaly and Dundee, 1986), undergoing a fixed short operation under a standard anaesthetic. Meptazinol and nalbuphine are highly emetic opioids and not widely used for premedication. We report here a similar randomized study with the more widely used pethidine 100 mg, a drug with an early onset but short duration of emetic action (Dundee, Clarke and Loan, 1965).

The method was identical to the studies referred to above, except that there were 30 patients in each group. One of these had 5 min of manual acupuncture following i.m. administration of the premedication, the other acting as a control. The subsequent anaesthesia was with methohexitone–nitrous oxide–oxygen. The times of observations are given in table XI.

Results are summarized in table XI.

TABLE XI. *Incidence of vomiting with or without nausea (V) and nausea alone (N) at the various study times, in patients premedicated with pethidine 100 mg, with and without subsequent acupuncture*

	No acupunture			Acupuncture		
	V	N	—	V	N	—
Before op.						
20 min	2	6	22	0	5	25
40 min	3	8	19	0	1	29
60 min	1	6	23	0	1	29
90 min	1	4	25	0	1	29
Total	4	9	17	0	6	24
After op.						
0–1 h	6	3	21	3	0	27
1–6 h	6	5	19	4	1	25
Total	9	5	16	4	1	25

There was a significant ($P < 0.05$) overall reduction in both pre- and postoperative emetic sequelae in patients receiving acupuncture, compared with the controls. This also applied to total perioperative emetic sequelae which occurred in 17 patients who received pethidine alone, compared with nine when this was accompanied by acupuncture.

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SIMPLE FEED-BACK CONTROL OF NEUROMUSCULAR BLOCK

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The Datex relaxograph measures the electromyographic response to standard train-of-four stimulation. It processes the raw EMG signal to give the current T1 as a percentage of the unparalysed T1 and the current T4 as a percentage of the current T1. A high-output alarm can be set to respond audibly when T1 exceeds a chosen value. This also emits a 5-V signal from the output port of the relaxograph, and this signal is maintained until the T1 again decreases below the alarm limit.

We have used this signal to trigger an Injectomat S-2 syringe pump so that it can deliver a short infusion of neuromuscular blocker. This is done through a controlling box of electronics the settings of which govern (i) the latency of triggering after the appearance of the high-output alarm signal, (ii) the duration of the infusion and (iii) the duration of an "inhibit" period after the end of the infusion during which the system remains refractory to a new or continuing high alarm signal.

We usually set the latency so that the infusion will start 10 s after the T1 from two successive trains-of-four has exceeded the alarm limit. This is to avoid response to a false alarm from a spuriously high T1.

The speed of the infusion is set on the infusion pump at a conveniently high rate. The dose is then determined by the dilution of the blocker and the duration of the infusion. The "inhibit" period is used to ensure that the dose has enough time to have its effect before another dose is given.

The device can be set to give large doses, with considerable variations in response height in the relatively long intervals between, or small doses at relatively short intervals with much less variation in response height. The effects of the latter are closer to those of a continuous infusion.

If the doses are too small to suppress T1 and cancel the high alarm signal, they will be repeated at intervals determined by the setting of the inhibit time. The response will find a mean level above that of the high alarm setting.

The device is simple to use and is adequate for stable control of neuromuscular blockade to any desired level when using one of the newer non-depolarizing blockers of intermediate duration.

ISOFLURANE AS A SUPPLEMENT TO NITROUS OXIDE FOR CAESAREAN DELIVERY: COMPARISON WITH HALOTHANE

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The use of isoflurane in obstetric anaesthesia has been studied previously (Warren et al., 1983). We here report a randomized study comparing the maternal and neonatal effects of 0.5% halothane or 0.75% isoflurane as supplements to 50% nitrous oxide in oxygen for elective Caesarean section in 20 healthy parturients.

Patients were preoxygenated, for 3–4 min, before induction with thiopentone 4 mg kg^{-1} (pregnant body weight) up to 250 mg, followed by suxamethonium 100 mg for tracheal intubation. Half received halothane and the other half isoflurane An infusion of 0.1% suxamethonium provided neuromuscular blockade. Patients were ventilated with a tidal volume of 10 ml kg^{-1} at a rate of 12 b.p.m. with end tidal carbon dioxide, FI_{O_2} and inhalation agent inspired concentration being monitored.

The inhalation agent was maintained until skin closure, but the concentration of nitrous oxide was increased to 70% after delivery. Suxamethonium was discontinued at skin closure and oxygen administered until return of reflexes. The ECG, heart rate and arterial pressure were monitored throughout and maternal and neonatal blood-gas tensions and acid–base values were measured at time of delivery. Apgar scores were assigned on delivery. The surgeon graded uterine relaxation on a 10-point scale, ranging from 0 (nil) to 10 (uterine atony). This, with the blood loss and need for supplementary doses of oxytocin, gave a clinical assessment of uterine relaxation.

Groups were broadly comparable with respect to maternal age and weight and induction to incision to delivery intervals. Although slightly more babies were depressed at birth after halothane, the difference in the incidence was not significant for the two agents (table XII). Uterine relaxation was similar in the two groups and no patient required blood transfusion. Recovery time (oxygenation to response to commands) was significantly shorter ($P < 0.001$) in the isoflurane group. Maternal and neonatal blood-gas tensions and acid–base values at delivery were within normal limits in both groups. No patient had intraoperative recall.

TABLE XII. *Important findings in the two series*

	Halothane	Isoflurane
Apgar < 7 1 min	4	1
5 min	0	0
Supplementary oxytocin	4	2
Uterine relaxation (mean grade (range))	4.6 (3–7)	4.3 (3–5)
Recovery (s) (mean ± SEM)	330 ± 46.7	135 ± 18.0

Isoflurane is an acceptable substitute for halothane for Caesarean section and has a quicker recovery time.

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BOOK REVIEWS

The History of Blood Gases, Acids and Bases. By Poul Astrup and John W. Severinghaus. Published (1986) by Munksgaard, Copenhagen. Illustrated.

This beautifully illustrated book by Astrup and Severinghaus fills an important gap in the history of medicine. It begins with a description of the struggles of man to understand the nature of the barometric pressure, emphasizing the historical importance of Otto von Guericke's air-pump and the Magdeburg experiment. The story of the discovery of the composition of air and the process of combustion is delightfully told, including interesting details such as Joseph Priestley's advice on how to catch mice and keep them for experiments. The origins of scientific chemistry and the difficulty in bringing down the phlogiston theory are very instructively described, particularly the decisive role of Antoine Lavoisier.

The great controversies of the second half of the last century are well covered, such as the dispute between Edward Pfluger and Carl Ludwig about the active transport of gases in the lung. Here the reader is left with a clear view of the importance of German science at that time, and the role of European hostilities. Then there is the tragic story of Fritz Haber, the inventor of the pH electrode and of synthetic fertilizers. Although, during the First World War, Haber devoted himself to the production of war gases for the German army, this did not prevent him from being expelled by Hitler in the early 1930s for being a Jew.

The 1952 polio epidemic in Copenhagen naturally deserves a separate chapter, not least because Poul Astrup played such a crucial part in the medical team.

There are many splendid illustrations of apparatus and personal details about the great scientists.

The final chapter of the book is concerned with the development of apparatus since the early 1950s, and who better than Severinghaus to tell the story of the contributions made by himself, by Stow and by Clark.

In conclusion, Astrup and Severinghaus' book will be an important and charming addition to any medical library or anaesthetic department.

J. Ponte

Anaesthesia Review 3. By L. Kaufman. Published by Churchill Livingstone. Pp. 216; indexed; illustrated. Price £14.00.

There are several (and indeed some would say too many) publications of this type at the moment, ranging from *Clinics in Anaesthesiology* which deals with a specific topic in each issue, to the long established *Recent Advances* which deals comprehensively with varying subjects chosen by the editors. This book belongs to the latter type, but differs somewhat in that it aims to bridge the gap between the delay in up-to-date work being transposed from the journals to standard textbooks. The topics are, therefore, covered in a briefer fashion rather than being in-depth reviews and, as always, with multi-author publications there are variations in the standard of presentation.

The first four chapters deal with medical problems relating to anaesthesia, the first of these comprising a number of unrelated topics ranging from respiratory function in colitis to AIDS and hepatitis. Two separate chapters deal with opioid receptors and endorphins, which being young and rapidly expanding fields are difficult to review, but have been dealt with commendably. Another difficult field is that of assessment of brain function, which again is well covered, although not helped by the use of many abbreviations, which does not make reading easier. The history of muscle relaxants is reviewed briefly and the newer drugs assessed, as are the newer inhalation agents. There are two admirable discussions on blood transfusion and blood products, including the use of red cell substitutes in the form of perfluorocarbon emulsions and modified haemoglobin solutions. One chapter is devoted to obstetric anaesthesia and another to controversies in obstetric practice, although these could easily have been dealt with in one. Other subjects covered include gas exchange during anaesthesia, neurosurgical anaesthesia, burns and inhalation injury and resuscitation.

The editor admits that some repetition is inevitable. Thus AIDS, opioid receptors and problems with etomidate infusions are briefly discussed by more than one author. This is neither necessary nor should it be inevitable, and could be potentially confusing to examination candidates. The inclusion of an Appendix revising some of the material in *Anaesthesia Review 2* is also not necessary. Commendable as it is to be as up-to-date as possible, the additional information therein hardly seems worth the effort. However, if such an appendix appears in *Review 4*, the editor will undoubtedly point out that endotracheal is now tracheal, that the approved name of glycopyrrolate is glycopyrronium and that enflurane and isoflurane are not fluorinated hydrocarbons.

The success of books such as this depends very much on the editor's choice of subjects and authors, and his ability to persuade the latter to deliver their manuscripts on time. This has been achieved with this issue and resulted in a valuable addition to the literature. *Anaesthesia Review 3* has appeared rapidly after its predecessor and it is to be hoped that such quality can be maintained and will not be sacrificed in aiming for quantity.

M. Morgan

Current European Anaesthesiology, Vol. I (Yearbook of the European Academy of Anaesthesiology). Editor-in-Chief R. M. Jones, Published (1985) by J. Wiley & Sons. Pp. 297; indexed. Price £24.50

This, the first yearbook of the European Academy, contains summaries of more than 170 papers, culled from 22 European journals—some devoted entirely to anaesthesia and intensive care and some not (for example *Nuclear Medicine Communications*). The authors of the papers themselves provided the summaries, by invitation of the board of editors, and after each are appended comments by a reviewer or reviewers, some well known and some not so well known. The book is divided into five sections: pharmacology, medical problems, clinical practice, equipment and monitoring, and resuscitation and intensive care. The British contribution is considerable: the

Editor-in-Chief is British, as are about one-quarter of the reviewers, whilst close on one-half of the papers reviewed appeared in British journals, mainly the *British Journal of Anaesthesia* and *Anaesthesia*.

It is easy to criticize the selection of papers in a book such as this. However, there must have been formidable political considerations in the choice of the contributions and reviewers should probably abstain from the obvious questions of "Why did they include this?" and "Why did they exclude that?" A more positive approach would be to say that there must be something here to interest any practising anaesthetist, and probably a good deal of material which he has not come across before. It is a book to dip into rather than to read from cover to cover. The reviews are generally charitable and not over-critical; reviewers have generally resisted the temptation to show off at the expense of the original workers—an irritating habit once common in this sort of publication.

One is left with the impression that 1984, the year reviewed, was a year of very modest advance. Perhaps that is what must be expected from anaesthesia—little steps forward rather than great leaps. One is also left with the impression that European anaesthesia (or better continental anaesthesia) and British anaesthesia are very much more like each other than they were only a few years ago.

Most of us would, however, have to admit that General de Gaulle was right and that we are not really good Europeans. We still feel greater affinity with colleagues in the Commonwealth (old and new) and in the U.S.A. than we do with our colleagues on the continent of Europe. Perhaps this is merely the result of the fact that we are bad linguists. Anyway, any increase in the bonding between continental and British anaesthesia can only be good. In anaesthesia, as in medicine as a whole, there is a need for ties of all sorts. This book goes some way to strengthening them.

John Utting

Gas Mixing and Distribution in the Lung. Lung Biology in Health and Disease Series, Vol. 25. Edited by L. A. Engel and M. Paiva. Published by Marcel Dekker. Pp. 432; indexed; illustrated. Price $90.

Every anaesthetist knows that the composition of alveolar gas is not uniform in different anatomical regions of the lung. These differences occur partly because of regional differences in perfusion and partly because of non-uniformity in the mechanical properties, and thus the ventilation, of different parts of the lung. It is also well known that both of these factors are determined to a great extent by the effect of gravity on the lung. Thus regional inhomogeneity is well established and well known. What of stratified inhomogeneity? This addresses the more obscure question of different gas composition along the airway. It is evident that at the end of inspiration the composition of gas in the upper airway is quite different from that in the alveoli, and the concept of deadspace is familiar to anaesthetists. Until recent years, most practitioners believed that a tidal volume equal to, or smaller than, the deadspace would be very undesirable in terms of maintaining a normal alveolar ventilation. The wide publicity given to high frequency ventilation and its introduction to clinical practice has necessitated a revision of the concept of deadspace and raises the question of how perturbations in ventilation influence gas mixing between deadspace gas and alveolar gas. This book provides a mass of basic information on the effect of the branching anatomy of the lung on gas mixing and distribution in the airways.

It is particularly gratifying that almost every chapter alludes to the fundamental work of Gordon Cumming and Keith Horsfield. I was particularly fortunate to start my research career over 20 years ago under their direction in the Department of Medicine at Birmingham. It was a time, just as Claude Lenfant describes in his introduction, when regional and stratified inhomogeneity was the subject of unrelenting scientific debate and excitement. Developments in the early 1960s in the use of radioisotopes by Milic-Emili in Montreal effectively established, not only the fact of regional inhomogeneity, but the mechanism. This led to rapid expansion of knowledge of the factors determining regional inhomogeneity and they are well reviewed in the chapter by J. M. B. Hughes and T. C. Amis. This contains one of the main sections where anaesthetists will feel at home, although the term "closing volume" has been almost entirely purged from the whole book. The section by Ludwig Engel describes further studies of intraregional gas mixing, largely based on the traditional approach of analysing expired gas concentrations. The reviewer was gratified to read the section on alveolar ventilation at high frequency. This is a most useful chapter in which different gas transport models are presented in an easily readable manner. The remaining chapters review the physics of molecular diffusion, and the effect of lung anatomy on gas mixing and transport. The book concludes with a fascinating and beautifully illustrated account of gas mixing and distribution in birds and fish, which reminded me of that great work *On Growth & Form* by D'Arcy Thomson. He was the founding father of mathematics applied to biology and this book is a worthy successor.

This is certainly not a subject expanding at the speed of light, but it contains much that should be known by those of us who connect patients to mechanical ventilators. The editors have virtually ignored the anaesthetist consumer, but anyone in our specialty planning research in the field of high frequency ventilation should invest in a copy.

J. G. Jones

Non-Invasive Respiratory Monitoring. Edited by Nochomovitz and Cherniak. Published by Churchill Livingstone. Pp. 229; indexed; illustrated.

This book is the third in a series on "Contemporary Issues in Pulmonary Disease". The authors are all from centres in North America; only one author is an anaesthetist, the majority of the remainder being "pulmonologists".

Each of the 10 chapters represents a monograph of the chosen topic. The chapters cover items of potential interest to anaesthetists such as that on oximetry and one discussing transcutaneous monitoring of respiratory gases (transconjunctival estimation is not mentioned). Others on CT scanning or Ultrasound of the Pleura and Chest Wall would have little interest to other than experts in the field, who would not require this type of review.

In the Preface the editors state that "the authors were chosen to represent mainstream opinion in their respective fields". This has usually produced a chapter dealing with the history of the measurement or techniques (often referred to papers from the 1800s and in technical German) followed by data (and bias) from the author's laboratory. The vast majority of the references are from years earlier than 1983. The chapters are otherwise well written and illustrated.

One good point about reading articles from North America is that new acronyms keep appearing. For example, in the chapter on "Polysomnography for Breathing Disorders in

Sleep" patients are divided into those having disorders of sleep excess (DOES) and disorders of initiating and maintaining sleep (DIMS). The latter evokes memories of the 20-stone docker on 30 pints a day having his haemorrhoids treated!

The book may fulfil the editors' ambitions of being "useful to a wide variety of health professions managing respiratory disorder". However, for the anaesthetist it is neither good background reading nor are the few relevant chapters as comprehensive or up to date as those in the British and European literature.

D. Royston

Perinatal Anaesthesia. Contemporary Issues in Fetal and Neonatal Medicine 1. By J. W. Scanlon. Published by Blackwell Scientific Publications. Pp. 300; indexed; illustrated. Price £32.50.

The editor of this the first volume of the series is a well-known neonatologist and a Professor of paediatrics. The authorship is North American and the book is made up of a series of 11 well-referenced essays on subjects of topical interest. They relate principally to the effects that drugs and anaesthesia may have on neonates. Very little is directly about anaesthesia; and some of the authors have found it inappropriate to limit the scope of their text to suit the title.

The first chapter "Toxicokinetics of anesthetics and analgesics during labor" suffers I believe from the fact that the authors are neither pharmacologists nor users of the agents, and they stray from their remit somewhat to talk rather shakily about both pharmacology and use. Ether anaesthetics are stated to be hydrocarbons, most local anaesthetics to be aminobenzoic acid derivatives, and opioids and general anaesthetics to be associated with maternal hypoxaemia. Placental transfer is discussed theoretically and the same old inapplicable formula is trotted out, which omits all important determinants of transfer rate.

Chapter two, Psychoteratology, describes the effects of social and illicit drug use on the fetus; interesting but not anaesthesia! The third chapter on anaesthesia and maternal disease, gives us a quick romp through relevant aspects of medicine, though rather surprisingly omits respiratory disorders.

Chapter four, covering anaesthesia for surgery during pregnancy, states that, in 1971, 50000 pregnant women underwent surgery. Where? In the U.S.A.? North America? The world? We are told that to understand the effects of surgical anaesthesia on the materno-fetal unit would require detailed knowledge of the effects of paternal and maternal exposure to a wide variety of substances. Why? We are also told that "fetal *hemostasis* depends on a consistent supply of oxygenated blood to the placenta" (my italics). Is this an example of the transatlantic language barrier?

Chapter five on maternal medication and newborn behaviour gives us more language trouble with "conceptualized as" (thought to be; regarded as), "reflexive" (reflex), "normative" (normal) etc. This, however, is a very well researched and thorough review.

The sixth chapter, on regional anaesthesia, sets out to explain techniques; in other words the content is rather more what one would expect. However, descriptions are too brief to be of use to practising clinicians.

Next is an interesting account of fluid, electrolyte and glucose homeostasis and it contains clear clinical recommendations. There is a chapter on neonatal anaesthesia, which includes some perinatal anatomy and physiology and some useful practical guidelines. Some British anaesthetists would perhaps not agree that a circle system be used for controlled respiration, while the Mapelson (unspecified) is recommended for spontaneous respiration.

One chapter covers anaesthesia for high-risk obstetrics; this is straightforward and interesting. Nowhere in the book, however, are there clear instructions for ordinary general anaesthesia for emergency obstetrics. For example, one sentence in the whole book is devoted to antacid premedication.

Next come two strong chapters by authors who have contributed extensively to their subjects: "Endorphins" by Therese Abboud, and "Anesthesia for diabetics" by Sanjay Datta. Both these are useful and instructive, although the lack of editorial hand is noted in such sentences as "fetal lung maturity is considered to be matured". Both chapters cover much more than anaesthetic consideration.

I am an inveterate quibbler: I enjoyed this book, although I am uncertain who its audience should be. I am learning to generally put up with split infinitives, though I hope they are not going to really become catching, or I might begin to often write them myself....

F. Reynolds

Orofacial Pains: Classification, Diagnosis, Management, 3rd Edn. By W. E. Bell. Published by Year Book Medical Publishers, Inc. Pp. 420; indexed; illustrated. Price £49.50.

This book has been written by an oral surgeon primarily for oral/dental surgeons, but is also written for any doctor dealing with orofacial pain.

The language of the book is American, but there are three pages of definitions at the beginning of the book which are very helpful in understanding the neurologists' terminology.

The author begins by explaining "pain as a clinical syndrome," devoting his first chapter to the theme. Further chapters describe neural mechanism and pathways. Considerable space is devoted to a classification of orofacial pains and descriptions of the same.

The last 70 text pages of this book are devoted to clinical examination, diagnosis and management. This last section would appear to be of more use to the clinician than the first part, which is mainly neurological theory.

Dr Bell illustrates from his patients' notes. The actual typed notes are reasonably clear, but the print used on his clinic notes does not appear as clear as it might be, and the book would have benefited if one copy of the casenote had been in larger print.

In his chapter on temporomandibular joint pain, Dr Bell gives very few references to support his classification of this pain in view of the vast available literature on the subject. His division of this syndrome into "disc attachment pain", "retrodiscal pain", "capsular pain" and "arthritic pain", is not in accord with normal thought on the subject in the United Kingdom.

It is surprising to the reviewer that Dr Bell fails to mention the use of cryotherapy as a method of alleviating trigeminal neuralgia. As this is now the third edition of the book, one would expect that this method would have at least been mentioned.

This book has a place on the library shelves of those dealing with orofacial pains, but at £49.50 one would think twice before rushing out to purchase it.

J. Wallace

Pain Relief in Labour. A Handbook for Midwives, 5th Edn. By Donald D. Moir. Published by Churchill Livingstone. Pp. 196; indexed; illustrated. Price £4.50.

The fact that this book was first published 15 years ago and has already reached its fifth edition is a tribute, both to the enthusiasm of the author and to the rapidly changing patterns of practice in midwifery and obstetric anaesthesia and analgesia.

Like its predecessors, this latest edition is easily read and is very up-to-date with acupuncture and TENS both rating a mention as methods of analgesia during labour

The changing practice of obstetric anaesthesia is well catered for, with a new chapter devoted to extradural and spinal analgesia. A highlight of this chapter is a very clear and concise description of "how to do" an extradural and this would certainly be worthwhile reading for any midwife before witnessing a "live" demonstration of the technique in the labour suite. The chapter on local anaesthetics and regional analgesia allows for the increasing trend towards midwives performing and repairing episiotomy wounds. The method of infiltration analgesia for episiotomy is described and the adequacy of 0.5% or, at most, 1% solutions of local anaesthesia for infiltration is stressed. An excellent feature of the chapter is an easily interpreted table of upper dose limits (in mg and ml) of commonly used agents. There is also a short sub-section on signs of local anaesthetic toxicity and their first line management and, since midwives may be first to notice a change in the status of their patient, it is important that they recognize those signs which may result from local anaesthetic toxicity.

The reasons for the continued and disappointingly high contribution of anaesthesia towards maternal mortality are discussed in the chapter on general anaesthesia. "Failed intubation drill" is fully dealt with and the role of the experienced midwife in rendering help to the anaesthetist is well explained.

The final chapter is concerned with the resuscitation of the newborn, a subject which is now assuming greater importance to midwives, since there seems to be a trend away from attendance by paediatricians at "routine" operative delivery. An early section of the chapter is devoted to the cardiovascular and respiratory changes which take place at birth and I feel that some of the intended readership would find this rather complex. However, later sections deal with the assessment of the newborn, the treatment of asphyxia and the checking of the equipment required for resuscitation and these parts of the chapter are concise and clearly written.

The illustrative material consists of six tables and nine figures and I feel this is adequate for a book of this type. The inclusion of photographic material would have dramatically increased the price of the publication which, as it stands, represents extremely good value at £4.50.

One minor criticism is that there is no bibliography—apart from Chapter Two. A short list of references might have further increased the value of the chapter on extradurals and spinals, in particular, as a number of recent publications are available.

In summary, this little book is characterized throughout by the author's clear style of writing and concise descriptions of practical procedures. It should appeal to a wide readership of midwives, physiotherapists working in maternity units, junior obstetricians and, indeed, to junior anaesthetists about to commence their maternity rotation. As such, it deserves a place on the shelves of every obstetric hospital library.

W. T. Frame

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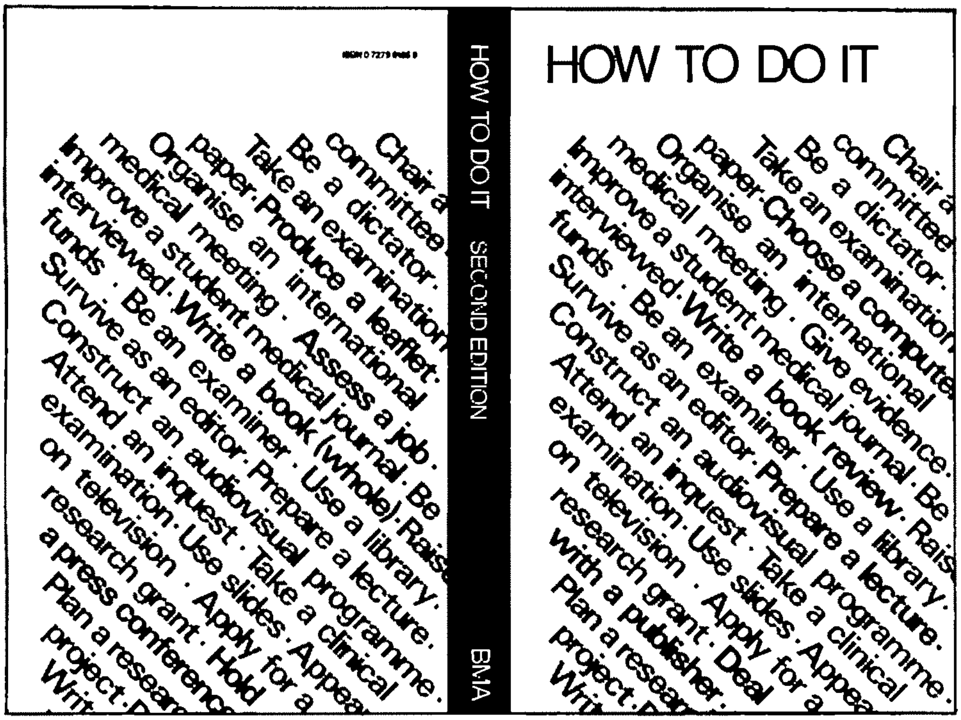

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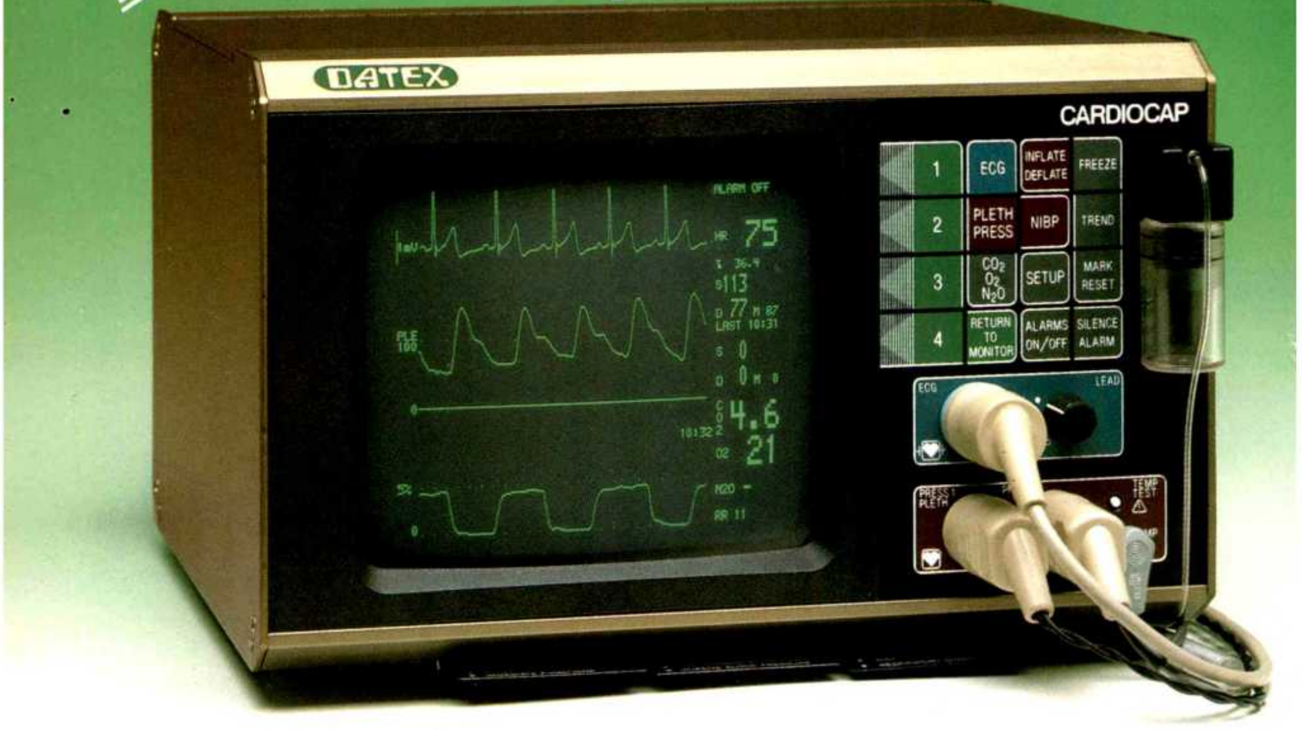

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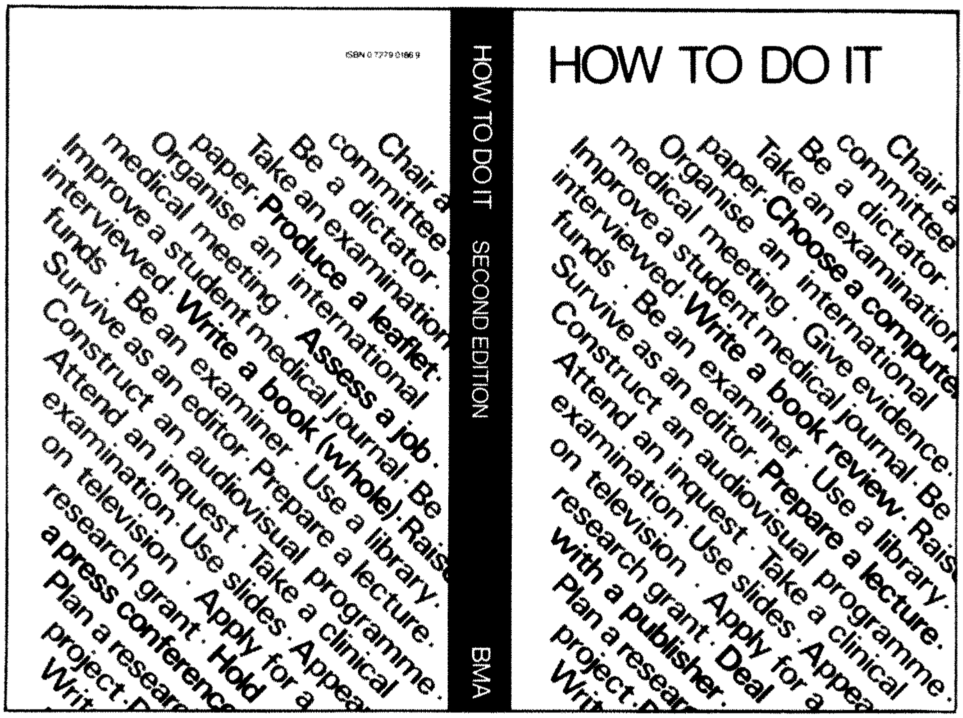
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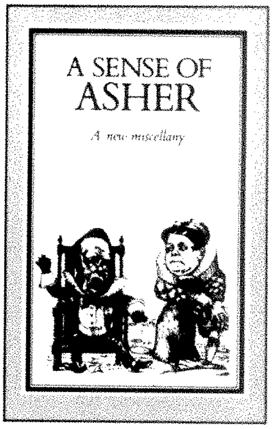

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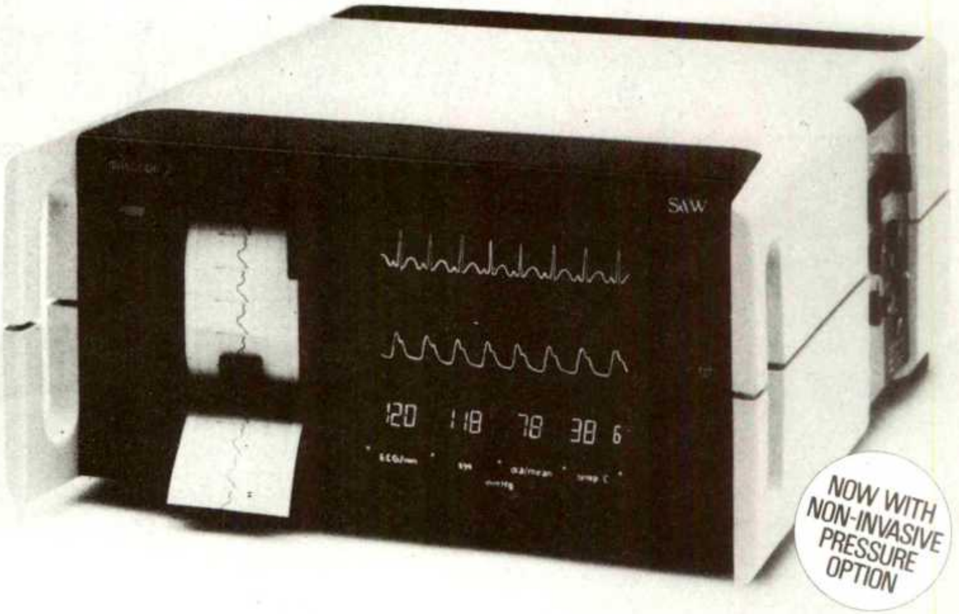

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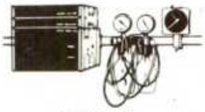

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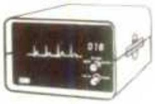

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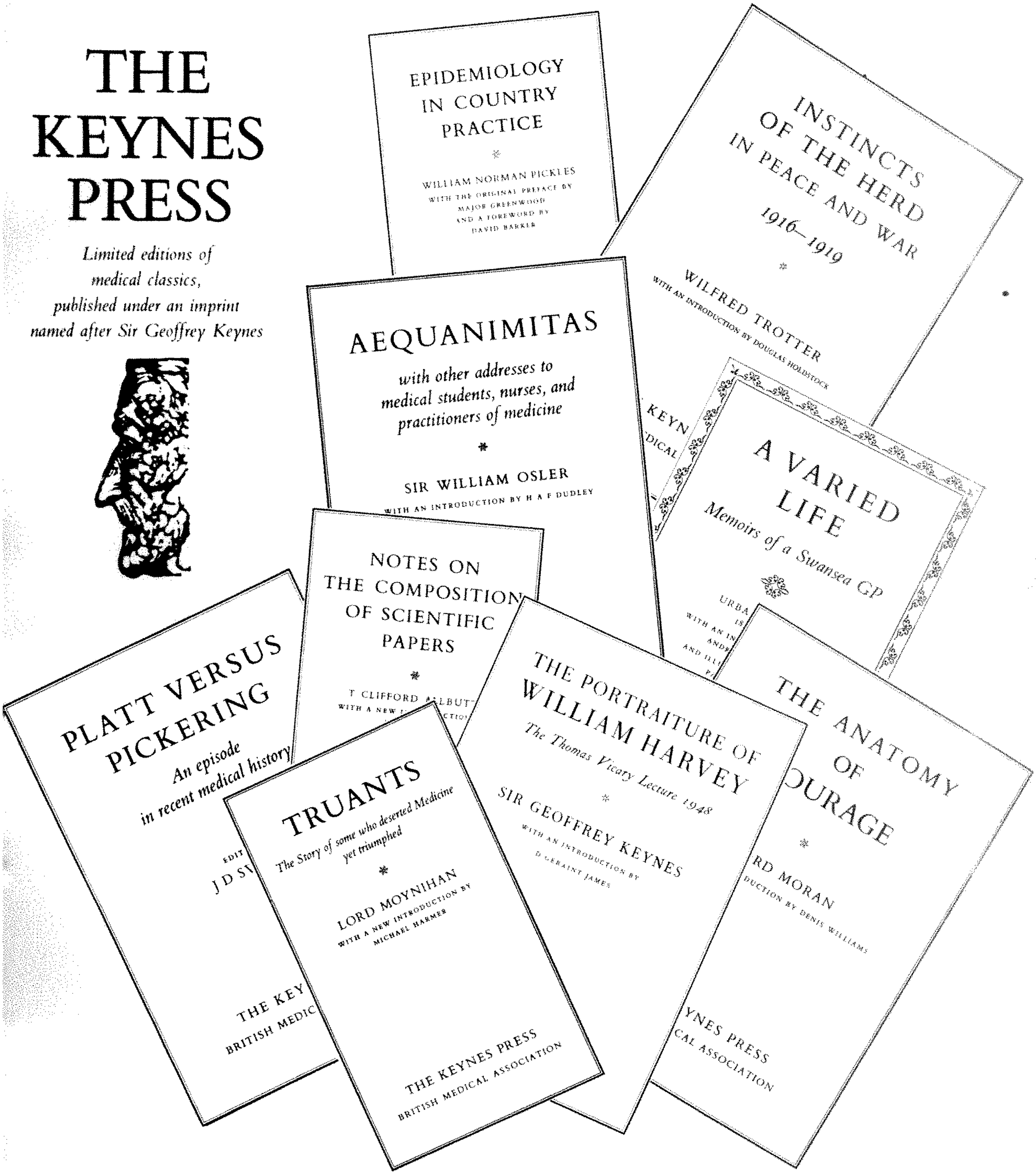
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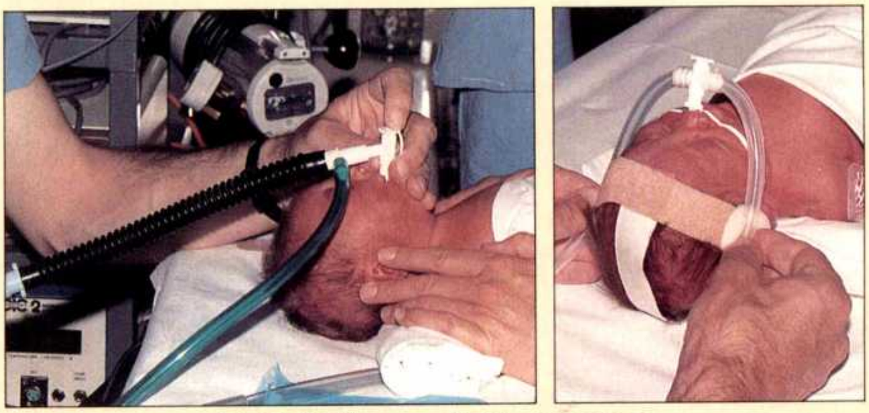

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EDITORIAL

HAEMATOLOGICAL CHANGES CAUSED BY NITROUS OXIDE

Cause for Concern?

There is now considerable evidence indicating that nitrous oxide oxidizes and inactivates vitamin B_{12} (when it is in the form of methyl cobalamin (Deacon et al., 1980)). Methyl cobalamin is the bound co-factor of the enzyme methionine synthetase, which is necessary for the re-synthesis of methionine (Chanarin, 1982). Furthermore, methionine plays an important role in the formation of deoxyribonucleic acid (Chanarin, 1982). Thus the depletion of methionine following nitrous oxide exposure is probably responsible for the megaloblastic anaemia and leucopoenia which follow exposure to the gas (Nunn, 1984).

The dyshaemopoietic effects of nitrous oxide after prolonged exposure have been well documented (Editorial, 1978) ever since the original fatal case report by Gormsen (1955), and can occur even at sub-anaesthetic concentrations.

It is the purpose of this article to examine critically the dyshaemopoietic effects of nitrous oxide in relation to its safety with respect to the patient in clinical practice. This is important, since bone-marrow depression appears to be the most common acute toxic effect of the gas which may have clinically important sequelae. Other untoward effects occur as a result of chronic abuse or pollutant exposure, or rarely in association with specific pathological or predisposing conditions (Chanarin, 1982) which are usually readily identifiable.

Nitrous oxide has been used with good results as an analgesic agent for the treatment of postoperative pain following major surgery, and for the relief of the pain associated with myocardial ischaemia. The period of continuous application has been for up to 3 days (Gormsen, 1955). Amess and colleagues (1978) reported 22 patients who had undergone open heart surgery. Eight of these patients received approximately 50% nitrous oxide and 50% oxygen for 24 h (group 1), nine received 50% nitrous oxide and 50% oxygen for between 5 and 12 h (group 2) and five patients (control) received no nitrous oxide (group 3). All patients in group 1 showed megaloblastic marrow changes, only three patients in group 2 showed mild megaloblastic changes, while the control group showed normoblastic aspirates. These workers also conducted a deoxyuridine (dU) suppression test in all the patients studied. Nine of the 11 patients showing megaloblastic aspirate showed abnormal dU suppression tests. The abnormal dU suppression tests were identical to those found in vitamin B_{12} deficiency, but since all these patients had had normal serum vitamin B_{12} concentrations before exposure, these results indicated that the nitrous oxide had interfered with the function of the vitamin. None of the patients examined became leucopoenic, but all showed thrombocytopoenic peripheral blood smears. Two patients with abnormal dU suppression tests were studied 6 days after the administration of the nitrous oxide, and showed normoblastic marrow and normal dU suppression tests, but now showed megaloblastic granulocytic changes.

Skacel and coworkers (1981) examined seven patients who had received 70% nitrous oxide plus 30% oxygen for 24 h presumably before, during and after exposure. They found abnormal dU suppression tests and megaloblastic changes in all patients within 2 days. The patients became normoblastic between 2 and 7 days later. Three to four days after the first evidence of megaloblastosis was noted, leucopoenic changes were found in peripheral blood which peaked 7–9 days later. Serum folate concentration increased within hours of the nitrous oxide administration and there was a concomitant decrease in serum methionine concentrations. Similar findings have been reported by other workers in a group of patients who were severely ill and required intensive care (Amos et al., 1982). All these individuals had received anaesthetic concentrations of nitrous oxide during surgery; however, the exact concentrations are not stated. Megaloblastic changes occurred in some of these severely ill patients with exposures to nitrous oxide of as little as 2 h. An interesting finding in this study was, however, that there was a greater correlation between the severity of illness and megaloblastic changes than with duration of exposure to nitrous oxide. It should be noted in this context that megaloblastic haemopoiesis with severe thrombocytopoenia has been previously reported in severely ill patients requiring intensive care but who had not received nitrous oxide (Ibbotson, Colvin and Colvin, 1975; Beard, Hatipov and Hamer, 1978). Two episodes of megaloblastic haemopoiesis have been reported in a single patient who was exposed to intermittent 50% nitrous oxide/oxygen mixtures in the first instance for 15–20 min, three times per day (aggregate exposure 13 h over 24 days) and in the second instance twice daily (aggregate exposure of 9 h over 14 days) (Nunn et al., 1982). The dU suppression test was abnormal on the first occasion only, but megaloblastic marrow aspirates were obtained during both exposures, which returned to normal 1 week after cessation of nitrous oxide administration (Nunn et al., 1982).

The findings presented above provide good evidence that exposure to nitrous oxide has detrimental effects on haemopoiesis. This effect may, however, be concentration dependent and may not always follow. Thompson and Lown (1976) using a concentration of 35% nitrous oxide in 65% oxygen in seven patients for protracted periods were unable to show any evidence of megaloblastic changes in peripheral blood smears. These subjects had received the gases for longer than 48 h for the control of ischaemic myocardial pain. In aggreement with these findings, Petrovsky and Yufuni (1962, 1965) were unable to demonstrate haematological changes following the use of nitrous oxide (30–70% in oxygen) for up to 24 h in 103 patients. These observations were corroborated by Fink (1967), who visited their clinic in Moscow.

Furthermore, in fit patients undergoing elective surgery a period of at least 5–6 h of exposure to 50% nitrous oxide in 50% oxygen is required before changes in bone marrow, as assessed by morphology and the dU suppression test, occur (Kano et al., 1981; O'Sullivan et al., 1981). In the O'Sullivan study a group of patients received nitrous oxide–oxygen mixtures for 24 h. These patients showed abnormal dU suppression tests and megaloblastic bone marrow changes which began to resolve 12 h after nitrous oxide was stopped. It must be stressed that patients ($n = 6$) who received nitrous oxide for periods ranging from 1 to 6 h had no evidence of dyshaemopoiesis, including normal dU suppression tests. Moreover, in a study of chronic alcoholic subjects no statistical difference could be found in peripheral blood smears (examined for evidence of megaloblastic changes before and for 7 days after exposure) between those who had received analgesic nitrous oxide (for 20–60 min; $n = 20$) and a control group who had not been treated with the gas (Gillman, 1986b).

A crucial finding in the study by O'Sullivan's group (1981) and confirmed by others (Skacel et al., 1982; Amos et al., 1984) was that folinic acid given before operation could prevent the development of bone marrow abnormalities in most patients exposed to nitrous oxide for lengthy periods during anaesthesia.

Kripke and Hechtman (1972) used nitrous oxide to wean a patient off a pentazocine addiction. This patient received nitrous oxide at concentrations of between 15% and 20% as follows: 24 h for 30 consecutive days; 18 h for the next 15 days; and 6 h for the remaining 202 days. Thus she received intermittent doses of nitrous oxide on each of 247 consecutive days. It is important to note that the patient had been maintained on a multivitamin regimen which included vitamin B complex and folic acid during her stay in hospital. However, this was discontinued on her discharge from hospital. Sometime after discharge (92nd day after treatment) she developed a folate deficiency which was diagnosed on the basis of the presence of an increased mean corpuscular volume (MCV) and hypersegmentation of polymorphonuclear leucocytes. This responded to folate supplementation on the 99th day by an increase in reticulocyte count and disappearance of hypersegmentation of the leucocytes. Two months later, the patient developed a neuropathy indicative of a multiple vitamin B (including vitamin B_{12} deficiency). Vitamin B complex therapy was restarted and by day 178 the neurological signs had returned to normal. It is most significant that the blood changes and neuropathy responded to vitamin supplementation despite the continued administration of nitrous oxide. These workers concluded that the pathological changes were secondary to vitamin deficiency and not the administration of nitrous oxide. Further evidence supporting this conclusion was the leucocytic response (up to 20000) which occurred concomitant with an attack of bronchopneumonia. The occurrence of a leucocytosis is not consistent with nitrous oxide depression of bone marrow, which is usually accompanied by leucopoenia (Chanarin, 1982).

Another interesting fact that has not previously been highlighted in the literature is that in only two patients (out of 32) who were heavy long-term abusers of nitrous oxide (suffering from myeloneuropathy), were peripheral blood examinations found to be abnormal on admission (Gillman, 1986a). Interestingly, of the two patients showing megaloblastic changes (Blanco and Peters, 1983; Gillman, 1986a). The one reported by Blanco and Peters (Layzer, 1978), showed an absolute deficiency of vitamin B_{12}, which may well have responded to supplementation as did the patient reported by Kripke and Hechtman (1972). This puzzling finding may indicate that with heavy intermittent exposure to nitrous oxide, the body is able, somehow, to overcome the dyshaemopoietic effects of nitrous oxide. Evidence for such a homeostatic mechanism is provided by animal work. Intermittent exposures to 40% nitrous oxide in oxygen produced myelotoxic changes (hypocellularity of the erythroid, myeloid, and lymphoid series, with vacuolization of myeloid precursors and decreases in numbers of mature myeloid forms) in rats at day 3 through to day 10 which did not reappear despite similar exposure for a further 25 days (Kripke et al., 1977).

Thus there seems to be a homeostatic mechanism that protects both man and rodent from the ravages of nitrous oxide bone marrow toxicity when exposed intermittently to analgesic concentrations (Gillman, 1986a). Perhaps this is an evolutionary protective mechanism that has occurred through the aeons, since nitrous oxide has been present in the atmosphere since and before the dawn of life (Miller and Urey, 1959). Such a protective mechanism could have been of some importance, since there is evidence that nitrous oxide is the primordial opioid substance (Gillman and Lichtigfeld, 1986).

It is clear from the material reviewed above that a minimum of 5 h of exposure to 50% nitrous oxide is required in uncompromized patients before evidence of bone-marrow dysfunction becomes demonstrable as assessed by morphological changes in marrow aspirates and the dU suppression test (Kano et al., 1981; O'Sullivan et al., 1981). Furthermore, in many cases, even after exposures of 24 h or longer, peripheral blood smears have failed to give morphological evidence of any untoward effects on erythrocytes, leucocytes or thrombocytes (Petrovsky and Yufuni, 1962, 1965; Fink, 1967; Thompson and Lown, 1976). Apart from this, where changes have been demonstrated, these resolve spontaneously within 10 days (Chanarin, 1982). Debilitated patients may be more susceptible (Amos et al., 1982): changes may in some such patients follow after as little as 1 h of exposure. However, this has by no means been unequivocally proved (Editorial, 1982). Moreover, adequate folinic acid supplements appear to provide good protection against the myelosuppressive changes caused by the gas (O'Sullivan et al., 1981; Skacel et al., 1982; Amos et al., 1984), even when it is administered for considerably longer than 6 h. Despite the apparent haematological dangers associated with the use of nitrous oxide, it has had a remarkable record of safety for over a century. This applies to both medical and dental indications. Nitrous oxide, like any other drug should be used with care and circumspection, in which case it can still be considered an extremely useful as well as safe analgesic (Gillman, 1986c) and anaesthetic agent (Gillman, 1982).

M. A. Gillman

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NITROUS OXIDE IN NEUROSURGICAL ANAESTHESIA

At the Sixth International Conference on Intracranial Pressure, held recently in Glasgow, the adverse effects of nitrous oxide on cerebrovascular haemodynamics were highlighted. Albin, Bunegin and Gelineau (1986) demonstrated, in dogs with increased intracranial pressure (ICP), that isoflurane, vaporized with nitrous oxide in oxygen, increased cerebral blood flow (CBF) even in the presence of hypocapnia and they postulated that this may place the brain at risk under conditions when intracranial hypertension is present. CBF and ICP decreased significantly in the hyperventilated dog given isoflurane (at 1.0 MAC) vaporized with 100% oxygen. More than 20 years ago McDowall, Harper and Jacobson (1963) observed a decrease in canine CBF at normocapnia when halothane was vaporized with air. McDowall and Harper (1965) confirmed this finding; when nitrous oxide in oxygen was introduced in place of air, CBF increased above the control value and decreased when it was withdrawn. Sakabe and co-workers (1976) showed, in man, that the addition of nitrous oxide to a background halothane anaesthetic significantly increased CBF equivalent. A recent study in rats demonstrated that the addition of nitrous oxide to background halothane anaesthesia was associated with dilatation of cerebral vasculature and increase in ICP (Seyde, Ellis and Longnecker, 1986).

Nitrous oxide is a cerebral circulatory and metabolic stimulant (Theye and Michenfelder, 1968; Sakabe et al., 1978) and this has been confirmed by the simultaneous measurement of CBF using direct and Kety Schmidt methods in the dog (Oshita et al., 1979). These undesirable effects of nitrous oxide can sometimes be overcome by the simultaneous adminstration of cerebral metabolic depressant drugs like the barbiturates, but a study on hypoxia survival time in mice revealed that nitrous oxide ablated the protective effect of thiopentone (Hartung and Cottrell, 1985).

It is tempting to suggest that there may be species variation. Carlsson and his colleagues (1976) showed that the administration of nitrous oxide to rats, sedated or anaesthetized with diazepam, resulted in decreases in both CBF and cerebral metabolic rate for oxygen ($CMRo_2$), yet they could not demonstrate a decrease in $CMRo_2$ with diazepam alone. However, in contrast, both CBF and $CMRo_2$ were decreased in the same species when midazolam was infused i.v. and this study also revealed that the addition of nitrous oxide significantly stimulated brain metabolism (Hoffman, Miletich and Albrecht, 1986).

Although it is likely that neuroanaesthetists will continue to administer nitrous oxide, there may be specific reasons for avoiding it. It is nearly always withdrawn in the presence of air embolism to prevent the amplification of the embolized air, but some prefer to use an air technique from the start of anaesthesia, in the sitting or steep head-up position. It may be avoided for the same reason when a pneumoencephalocoele is present. Prevention of pollution may be another reason for eschewing nitrous oxide; operations frequently last in excess of 4 h, which may result in vitamin B_{12} inactivation, although there has not been confirmation of this in man.

I believe that the continuous i.v. infusion of hypnotic and analgesic agents can be suitable alternatives to techniques of anaesthesia using nitrous oxide in oxygen. Steady drug concentrations are achieved within a therapeutic band, thus avoiding fluctuating plasma and tissue concentrations which follow bolus injections. Requirements are less, recovery is not excessively delayed and there is less likelihood of postoperative respiratory depression.

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RADIOGRAPHIC STUDY OF INTERCOSTAL NERVE BLOCKADE IN HEALTHY VOLUNTEERS

A. W. A. CROSSLEY AND H. E. HOSIE

SUMMARY

The spread of solutions injected to the intercostal space was studied in 10 healthy volunteers. Up to 20 ml of a 50:50 mixture of local anaesthetic solution and a radiopaque dye was injected through a modified extradural catheter placed in an intercostal space at the posterior angle of the rib. Radiographic films demonstrated spread by an extrapleural route into adjacent intercostal spaces and this was confirmed by the occurrence of analgesia in the corresponding dermatomes. The relevance of these results to clinical practice is discussed.

Intercostal nerve blockade, performed by multiple injections to adjacent intercostal spaces, has an established role in providing analgesia over an extensive field for upper abdominal and thoracic surgery. Recently, a number of authors have reported the successful maintenance of intercostal blockade over a prolonged period by the insertion of a catheter to a single intercostal space and repeated "top-up" injections using large volumes of local anaesthetic. In this way, anaesthesia has been maintained for up to 4 days in a patient with multiple rib fractures (O'Kelly and Garry, 1981), and over a period of 48 h in patients recovering from cholecystectomy (Murphy, 1983).

The interest in this technique has stemmed from the report of Nunn and Slavin (1980) that india ink, injected at the posterior angle of the rib in cadavers, spread through the flimsy substance of the intercostalis intima muscle to gain access to an extrapleural potential space and, hence, to the neurovascular bundles of intercostal spaces adjacent to that injected. This result has been confirmed directly by Murphy (1984), but has been disputed in radiographic studies in patients, and in cadaver studies using both ink and latex to define the space injected (Moore, Bush and Scurlock, 1980; Moore, 1981), and the debate about the route of spread of local anaesthetic solutions in the intercostal space continues (Moore, 1985; Murphy, 1985).

We have attempted to resolve this controversy by performing a radiographic study, in healthy volunteers, of the spread which occurs when a local anaesthetic solution is injected via a catheter to the intercostal space. Some of these results have been presented to the Anaesthetic Research Society (Hosie and Crossley, 1986).

SUBJECTS AND METHOD

Approval for the study was obtained from the local Ethics Committee. Informed consent was obtained from 10 volunteers (ASA group I) aged between 23 and 30 years who gave no history of allergy or hypersensitivity to local anaesthetics. All of the volunteers were medically qualified. The catheters used were modified by removing the distal 5 cm, to leave a catheter with a single end hole.

An 18-gauge i.v. catheter (Quik-Cath) was inserted to a vein in the dorsum of the non-dominant hand in each volunteer, and heart rate and arterial pressure were measured. The volunteer was then placed in the left lateral position, with the right arm widely abducted. Under aseptic conditions, the 7th right intercostal nerve was anaesthetized in the conventional

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manner at the posterior angle of the rib, by advancing a 23-gauge needle off the lower border of the rib into the intercostal space perpendicular to the skin, and subsequently injecting 1% lignocaine 2 ml. The muscles and skin overlying the space were anaesthetized by infiltration as the needle was withdrawn. This procedure established a "safe" depth, to which a Tuohy needle was advanced into the space using the same perpendicular approach. The bevel of the Tuohy needle was directed laterally and an 18-gauge radiopaque extradural catheter (Portex Minipack) was inserted to the intercostal space until a 3–5 cm length was beyond the skin. In successfully placed catheters, moderate resistance to insertion was experienced. In some subjects difficulty was encountered in accurately identifying the 7th intercostal space, and the catheter was inadvertently inserted to an adjacent space. The consistency with which the target space was achieved improved as the study progressed.

After insertion of the catheter, the subjects were taken to the radiology department where a total of 20 ml of a 1:1 mixture of iopamidol (Niopam 300) and 2% lignocaine with adrenaline 1:200000 was injected through the catheter in increments of 5 ml, 5 ml and 10 ml, with the subject standing. Two minutes after each increment, a posteroanterior chest x-ray was obtained, and after the final increment a lateral chest x-ray was taken. In some subjects, a lateral decubitus film was also obtained. No subject required a total of more than five films.

After administration of the final increment of anaesthetic with dye, arterial pressure and heart rate were recorded at regular intervals. The developing analgesia was determined by pin-prick and recorded on a dermatomal map.

A consultant radiologist reviewed the posteroanterior and lateral chest radiographs taken after the final increment and predicted the extent of the analgesia obtained from the observed distribution of the contrast medium. She was unaware of the analgesia obtained in each subject, and was asked to assume that all areas between the upper and lower extents of the dye observed would be analgesic. The radiologist also gave advice on the interpretation of the lateral decubitus films.

RESULTS

The results of the nine successful blocks performed are summarized in table I. Following

TABLE I. *Summary of results. Analgesia predicted is the field predicted from the x-ray appearance. Analgesia obtained is that mapped by pin-prick at the maximum extent of the block*

Subject	Type of spread	Catheter position	Analgesia obtained	Analgesia predicted
1	Extrapleural + paravertebral	T8	T8–T10	T8–T10
2	Extrapleural + paravertebral	T9	T8–T11	T8–T10
3	Extrapleural + paravertebral	T8	T7–T10	T7–T10
4	Extrapleural + paravertebral	T7	T6–T10	T6–T10
5	Extrapleural + paravertebral	T8	T6–T9	T7–T10
6	Extrapleural alone	T8	T8–T11	T7–T10
7	Extrapleural alone	T7	T5–T8	T6–T8
8	Paravertebral alone	T6	T5–T8	T6–T8
9	Paravertebral alone	T6	T4–T8	T5–T7

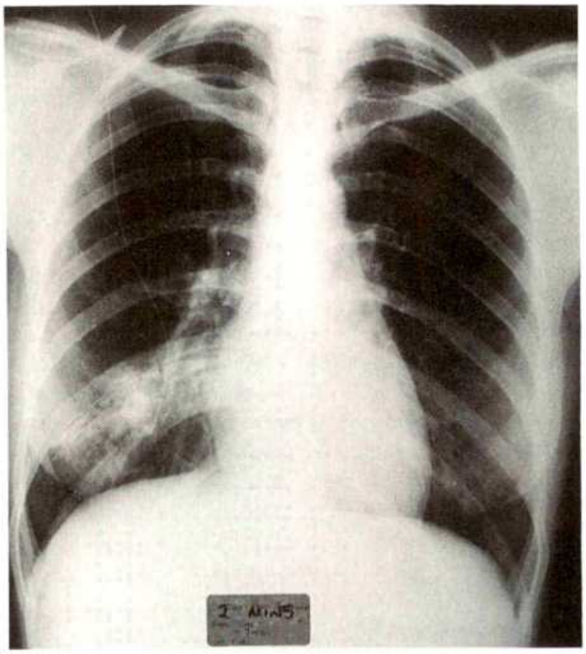

FIG. 1. An erect posteroanterior chest radiograph of a female subject following intercostal catheterization and the injection of 5 ml of the local anaesthetic–dye mixture. The catheter can be seen entering the right 9th intercostal space, and contrast is seen around the tip of the catheter and extending horizontally through the intercostal space.

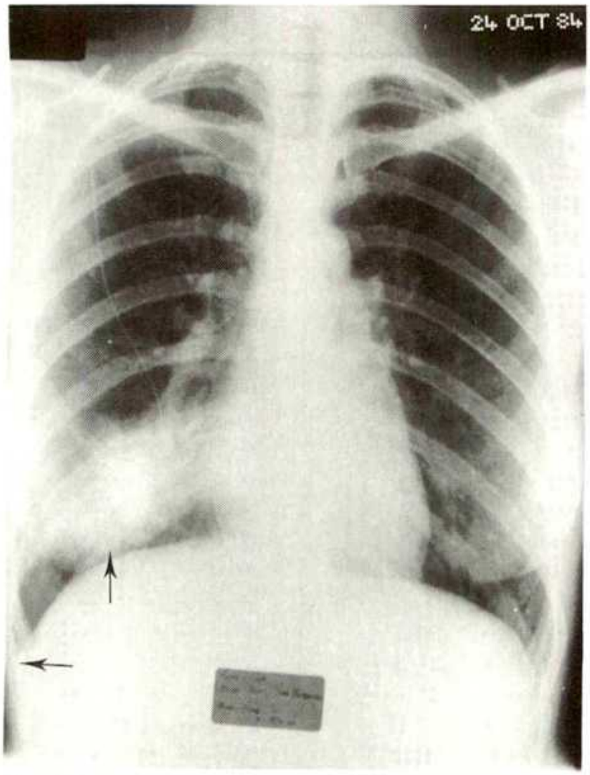

FIG. 2. An erect posteroanterior chest radiograph of the same subject as in figure 1, following the injection of 20 ml of the local anaesthetic–dye mixture. Contrast now extends medially through the 9th intercostal space to the paravertebral space, and further contrast is visible in the right costophrenic angle (arrows). Since the appearance of the accumulation at the costophrenic angle did not change on lateral decubitus films, this appearance was taken as indicating extrapleural spread.

the injection of 5 ml of the local anaesthetic–dye mixture, the dye was confined to the intercostal space catheterized in all nine subjects (fig. 1). Injection of 20 ml of the mixture produced a distinctly different radiographic appearance, as reported below.

Radiological appearance

In five of the nine subjects, evidence was obtained of two routes of spread of the contrast and local anaesthetic mixture. In all five, dye was seen to have spread medially from the catheter tip along the intercostal space injected, reaching the paravertebral space in two subjects. Dye was also seen commonly in adjacent intercostal spaces, spreading in the same horizontal plane. A further accumulation of contrast was seen in the right costophrenic angle in all five subjects (fig. 2).

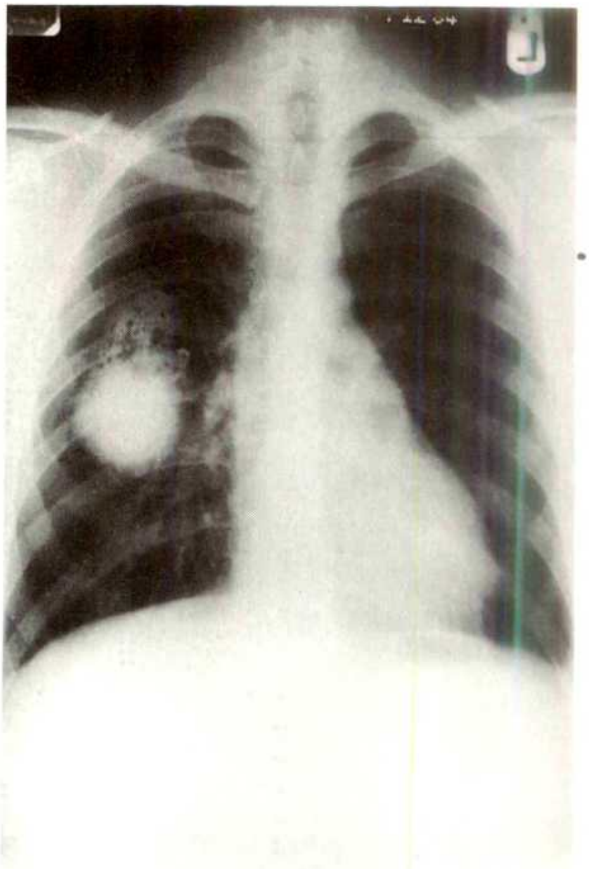

FIG. 3. An erect posteroanterior chest radiograph of a male subject following intercostal catheterization and injection of 20 ml of the local anaesthetic–dye mixture. The catheter tip is in the right 7th intercostal space, and is surrounded by a discrete mass of contrast medium, overlying the 7th and 8th intercostal spaces. There is no evidence of spread towards the paravertebral space, nor of contrast in the right costophrenic angle.

Lateral decubitus films taken in these subjects demonstrated that the pool of dye in the costophrenic angle was confined in an extrapleural space, since it was unaltered by posture. This appearance was taken as direct evidence of an extrapleural route of spread.

In another two of the nine subjects, contrast was seen around the catheter tip, and in one of these also in the costophrenic angle. In the second, the dye formed a discrete circular mass (fig. 3), and the lateral chest radiograph provided a dramatic demonstration of the extrapleural route of spread (fig. 4). In this film, the bolus of contrast could be clearly seen to be lifting the pleura off a

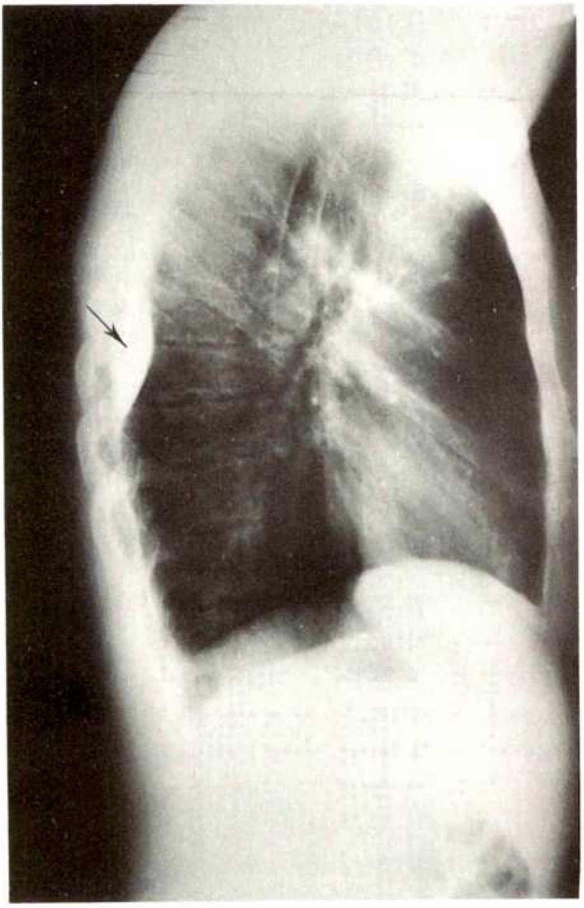

FIG. 4. A lateral chest radiograph taken immediately after that in figure 3, showing that the discrete mass of contrast is caused by the bolus in an extrapleural space separating the pleura from its attachments over a number of adjacent ribs (arrow).

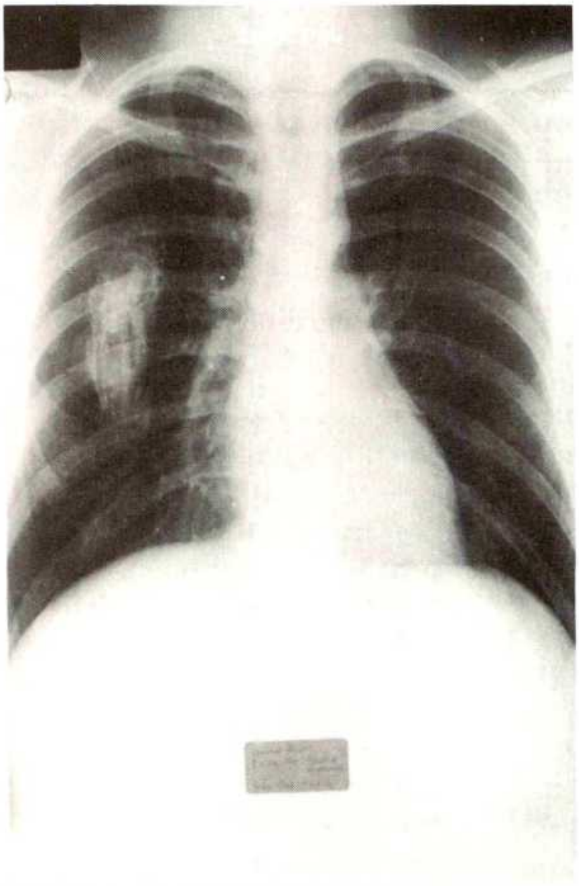

FIG. 5. A posteroanterior chest radiograph of a male subject following an attempt at intercostal catheterization and the injection of 10 ml of the local anaesthetic–dye mixture. The catheter tip is lying superficially to the 6th intercostal space, and is associated with a vertical distribution of the contrast medium. This appearance is not associated with analgesia.

number of adjacent ribs. Neither of these subjects showed any evidence of lateral or medial spread through the space catheterized.

In the two remaining subjects, contrast was observed only within the intercostal space injected, spreading medially to reach the paravertebral space. In these subjects, no evidence of extrapleural spread was obtained.

In three of our 10 subjects, initial attempts to catheterize the intercostal space failed. In two of these subjects, a subsequent attempt was successful. No attempt was made to repeat the third. All of the misplaced catheters were placed superficially in the muscles of the back, and the radiographic appearance associated with this is distinct (fig. 5). In these films, contrast is seen to be distributed in a vertical plane, with a typical striated appearance. No dye is seen lying horizontally in the intercostal space.

Analgesia

Analgesia typically extended over four adjacent dermatomes, to either side of the intercostal space catheterized. The onset of analgesia occurred within 5–15 min of the final increment, and its duration was 1–2 h.

Table I shows the analgesia obtained compared with that predicted by the radiologist. Calculation of Spearman's Rank Correlation Coefficient for these data yielded a value of $r_S = 0.91$ ($P < 0.01$).

Complications

No major complications of the technique were observed. One subject suffered a temporary neuritis within the distribution of the space catheterized, comprising an area of numbness and paraesthesia over the costal margin, and tenderness over the site of injection. This resolved completely and spontaneously over a period of 3 weeks. Two other subjects experienced transient light-headedness following the injection of lignocaine, without cardiovascular disturbance.

DISCUSSION

We have shown, using a radiographic method in healthy volunteers, that solutions injected to the intercostal space at the posterior angle of the rib spread by an extrapleural route to reach adjacent intercostal spaces. In most subjects there was also evidence of horizontal spread within the intercostal space towards the paravertebral space. These results clearly support the observations of Nunn and Slavin (1980) and Murphy (1984), who reported that solutions injected to the intercostal space reached an extrapleural space by passing through the flimsy substance of the intercostalis intima muscle.

It has been disputed that extrapleural spread of local anaesthetic solution occurs, on the basis of studies in which small volumes have been injected to the intercostal space (Moore, Bush and Scurlock, 1980; Moore, 1981). In the present study, we observed that, with small volumes such as 5 ml, spread as determined on the posteroanterior chest radiograph, is almost always confined to the intercostal space injected. Without the injection of further increments, our results may have resembled those of Moore, Bush and Scurlock (1980).

Unlike Johansson and Colleagues (1985) and Murphy (1983), who used the technique to provide analgesia after cholecystectomy, we experienced no difficulty in mapping analgesia by pin-prick in those volunteers in whom the catheter was correctly placed. A number of factors may explain this. All our volunteers were medically qualified, and so were familiar with the concept of mapping analgesia, whereas patients undoubtedly experience painful sensations originating from areas not covered by the block, such as the extreme ends of the wound, and visceral afferents. However, we were unable to map analgesia in those in whom the catheter was found to be lying superficial to the intercostal space, suggesting that correct placement of the catheter is a major factor. The distinct "tug" felt as the tip of the Tuohy needle pierces the posterior intercostal membrane has been suggested to be a sign of successful catheterization of the intercostal space (O'Kelly and Garry, 1981). Our experience would lead us to regard this as an unreliable sign, since a "tug" was felt in each of the unsuccessful attempts, as the Tuohy needle pierced the superficial muscles of the back.

Misplacement of the catheter was the most common complication of this small series. Few other complications were observed and, unlike Moore (1985), we would consider this technique as safe as many other local and regional techniques in routine use. No pneumothorax occurred in any subject. There was no evidence that the catheter tips migrated through the pleura into the pleural cavity, as suggested by Baxter, Flynn and Jennings (1984). The transient lightheadedness that occurred in two subjects might have been caused by the rapid increase in plasma concentrations of local anaesthetic that is known to follow intercostal nerve blockade (Tucker et al., 1972; Moore et al., 1976a, b). However, no other symptoms or signs of lignocaine toxicity occurred, and there was no cardiovascular disturbance. We would agree with Murphy (1985), that the use of repeated intercostal injections for the maintenance of prolonged analgesia is more likely to result in serious complications such as pneumothorax than is the single insertion of an 18-gauge Tuohy needle and catheter. It is our usual practice when performing any local or regional anaesthetic technique to have ready the means for resuscitation, as suggested by Moore (1985).

We believe that this technique is of value for the management of postoperative pain in selected patients, and for pain resulting from multiple rib fractures. The use of an intercostal catheter allows analgesia to be maintained over a wide field for a prolonged period, avoids repeated skin puncture, and deserves further investigation in a clinical setting.

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POSTOPERATIVE PARAVERTEBRAL BLOCKS FOR THORACIC SURGERY

A Radiological Appraisal

I. D. CONACHER AND M. KOKRI

Intercostal nerve blockade is a useful adjuvant technique for the relief of pain after thoracic operations (Moore, 1975). However, a series of blocks may be necessary to produce adequate analgesia of the skin. Prolongation of the duration of analgesia can be achieved with catheter techniques, and a system in which a single catheter is utilized would be a useful addition to the armamentarium of the thoracic anaesthetist since it would lend itself to continuous infusions of the kind used in association with extradural blockade (Conacher et al., 1983).

Several studies on cadavers (Nunn and Slavin, 1980; Moore, 1981) have demonstrated that the anatomical plane in which the intercostal nerve lies is contiguous with that above and below. This explains why an injection in one intercostal space may result in analgesia over several dermatomes. Medial spread of drug from the intercostal space is also likely, as far as the extradural space according to some reports (McIntosh and Mushin, 1947; Middaugh et al., 1985).

In 1979, Eason and Wyatt revitalized interest in the paravertebral space as a repository for catheters and local anaesthetic, and described the widespread, unilateral analgesia which could be achieved by the use of two catheters. Using the same approach, we have inserted a single catheter to a series of patients following a thoracic operation; in some, contrast medium was injected through the catheter.

SUMMARY

Five patients who underwent thoracic operations had an extradural catheter placed in the paravertebral space. X-ray contrast was injected through the catheters. In those who had detectable analgesia, contrast spread extensively, laterally, along one intercostal space, and up and down the paravertebral spaces. In one patient, contrast appears to have entered the extradural space and, in another who had no detectable analgesia, the contrast was probably dispersed intrapleurally. The significance of these findings is discussed.

PATIENTS AND METHODS

Five patients, detailed in table I, to whom the procedure had been explained, agreed to be studied. At the end of surgery, while they were anaesthetized and in the lateral thoracotomy position, a single extradural catheter was inserted paravertebrally just below the wound dressing and close to the level of the intercostal space through which the operation had been conducted—in all these patients, the 6th or 7th. The landmarks for the injection were as described by Eason and Wyatt (1979). The point of a short-bevel Crawford needle was sited 3 cm lateral to the top edge of a spinous process and 90° to the skin surface. The needle was inserted down on to a rib before being worked over its upper border. Recognition of entrance to the paravertebral space was with loss of resistance to the injection of physiological saline as the needle penetrated the costo-transverse ligament. After aspiration had shown neither air nor blood, an extradural catheter was inserted through the needle and advanced 2–3 cm into the space.

In the high-dependency recovery area, 0.25% bupivacaine 20–30 ml with 1:200000 adrenaline was injected through the catheter with the patient in a sitting position. Half an hour later, analgesia

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TABLE I. *Details of patients*

No.	Age (yr)	Sex	Lesion	Operation	Initial dose local anaesthetic	Dermatomal analgesia
1	62	M	Bronchial carcinoma	Right pneumonectomy	0.25% Bupivacaine 30 ml	Right T7–T10
2	43	F	Mediastinal sarcoma	Left thoracotomy	0.25% Bupivacaine 25 ml	Left T5–T9
3	32	F	Bronchial carcinoid	Left pneumonectomy	0.25% Bupivacaine 25 ml	Left T6–T11
4	26	F	Lymphoma	Left pneumonectomy	0.25% Bupivacaine 20 ml	Left T3–T10
5	67	M	Bronchial carcinoma	Right lobectomy	0.25% Bupivacaine 25 ml	None

was assessed with response to pin-prick, touch with ice, gentle pressure on the wound dressing, and light traction on the pleural drains so that the retaining skin sutures were put on a stretch.

All patients received additional analgesia in the form of a continuous low-dose i.v. infusion of papaveretum.

Later, immediately before the routine postoperative chest x-ray was taken, and with the patient in a sitting position, Iopamidol 10 ml (Niopam 300) was injected slowly via the catheter. No lateral-view x-rays were taken since they are not part of the postoperative routine within 12 h of operation.

RESULTS

In patients 1, 2, 3 and 4 there was evidence of unilateral loss of sensation to pin-prick and temperature discrimination in the dermatomal

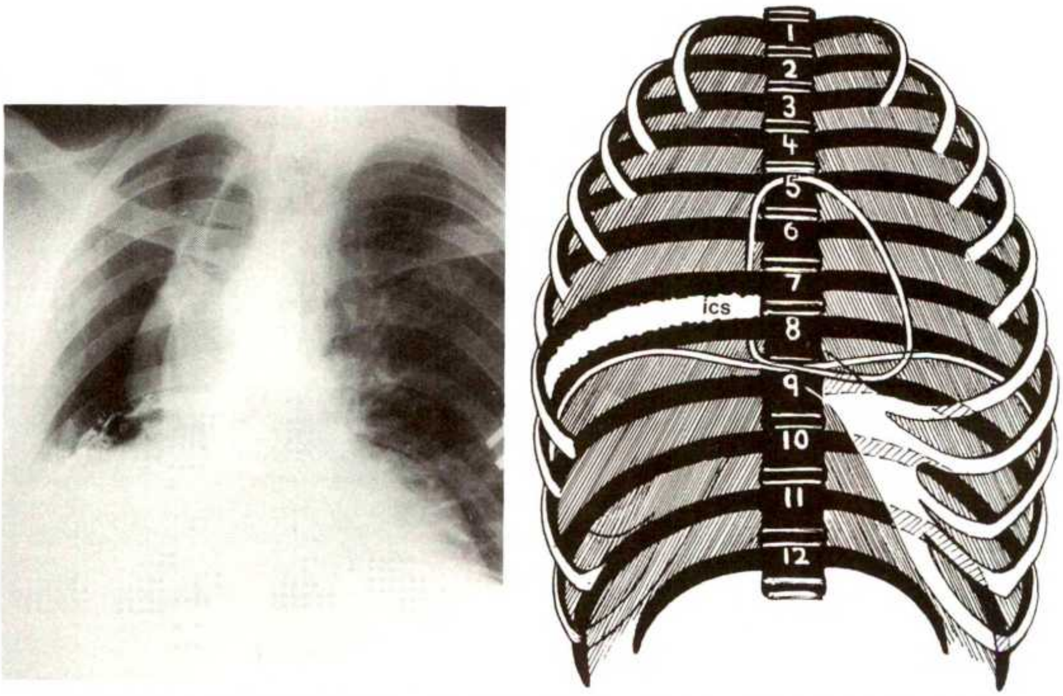

FIG. 1. Patient 1: radiograph, and diagrammatic representation of spread of contrast. ics = Intercostal space; ps = paravertebral space; es = extradural space; p = pleura.

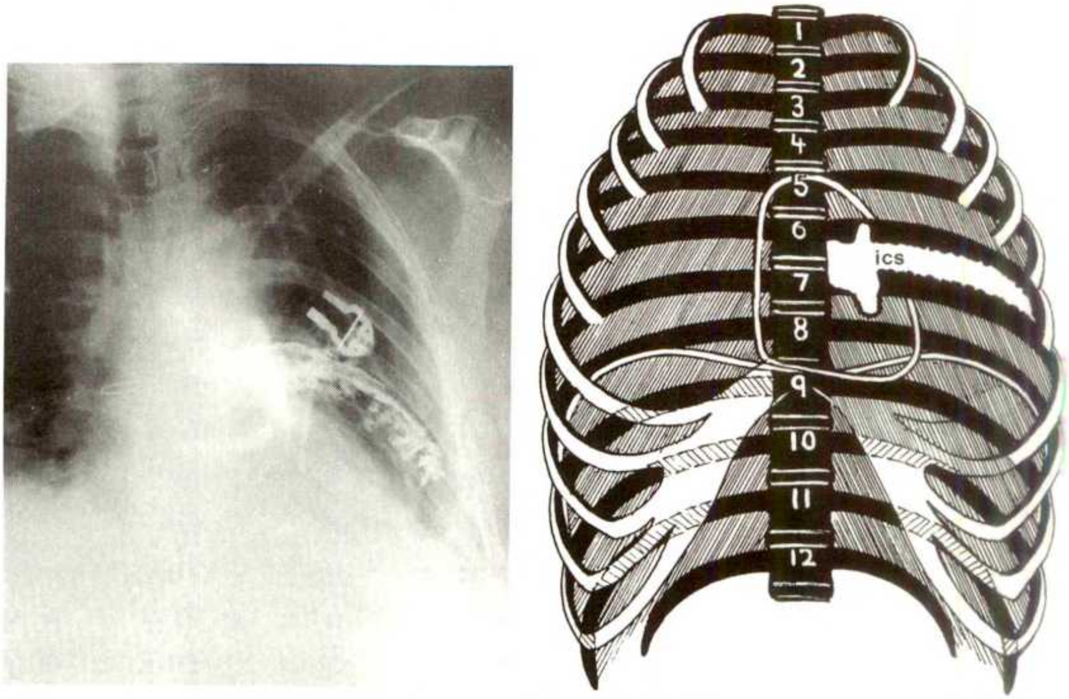

FIG. 2. Patient 2: radiograph, and diagram of spread of contrast.

distributions shown in table I. Patients 1, 2 and 3 were tender to gentle pressure on their wounds posteriorly where the incision reached into the region of the 3rd and 4th thoracic dermatomes and where there was no loss of sensation to pin-prick. Patient 2 was aware of traction on the skin when her anterior pleural drain was tugged. Patient 4 had slight discomfort on deep breathing. Patient 5 had no loss of sensation to any of the provocative test stimuli.

The anterior–posterior chest x-rays of each patient taken in the recovery area are reproduced—figure numbers 1–5 correspond to the patient numbers 1–5. Characteristically, in patients 1–4, there was marked spread of contrast laterally along a single intercostal space. In patient 1, further spread of contrast is not well delineated or depicted since it is concealed by fluid and a raised hemidiaphragm. In figure 2, contrast can just be distinguished to have spread both up and down from its prominent distribution in an intercostal space and, significantly, in a position well lateral to the vertebral bodies. In the third figure, contrast, although not well demonstrated, has moved into the paravertebral space above the site of injection and has spread in a paramedian band, parallel to the aortic shadow. There is a prominent "knuckle" of contrast two intercostal spaces lower. In the original x-ray, this paravertebral spread of contrast, as in patient 4, is well shown below the level of injection. Indeed, in both, contrast can be detected at least three spaces caudal to the level of the injection and extending, in patient 3, to below the diaphragm. In patient 4, however, there is cephalad spread of contrast. Here, beside a rib fractured during surgery, contrast can clearly be seen in the midline and up the right hand side as far as the third thoracic vertebra. It is probably in the extradural space.

In the x-ray of patient 5, the one who had no evidence of effective neurological blockade, the catheter is well outlined, but there is only a small volume of contrast visible and it appears to define no anatomical plane. The lack of clinical effect, as well as the rapid dispersal of contrast suggests that the catheter tip is intrapleural.

DISCUSSION

Lopamidol is a recently introduced, non-ionic, water soluble contrast medium which is rapidly excreted and is the agent of choice for myelo-

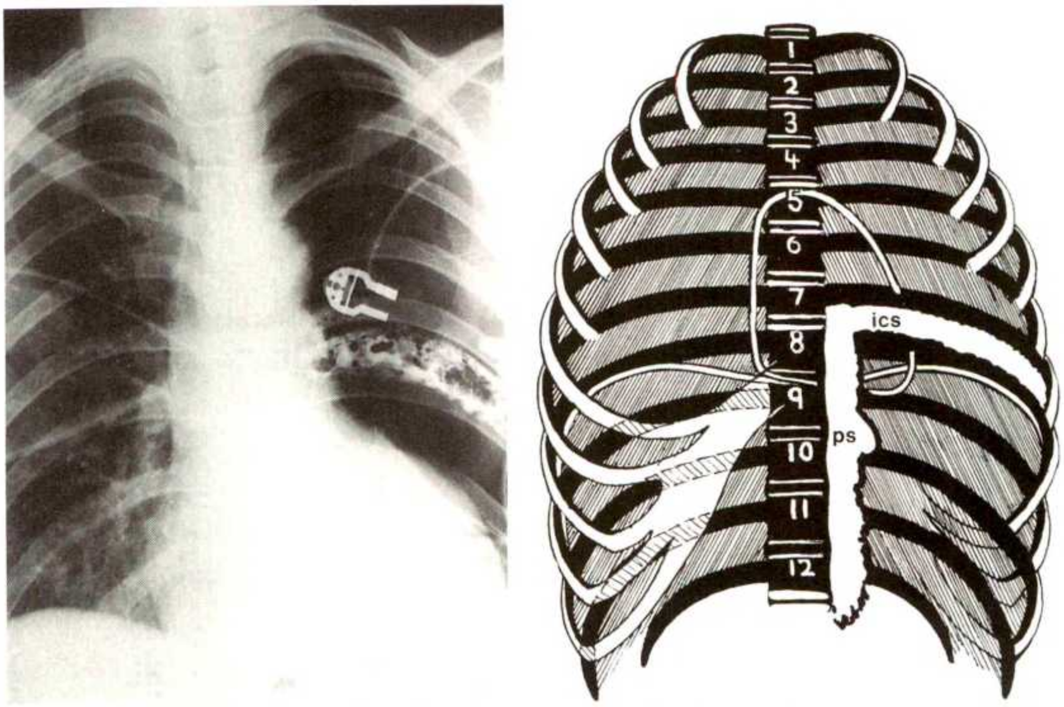

FIG. 3. Patient 3: radiograph, and diagram of spread of contrast.

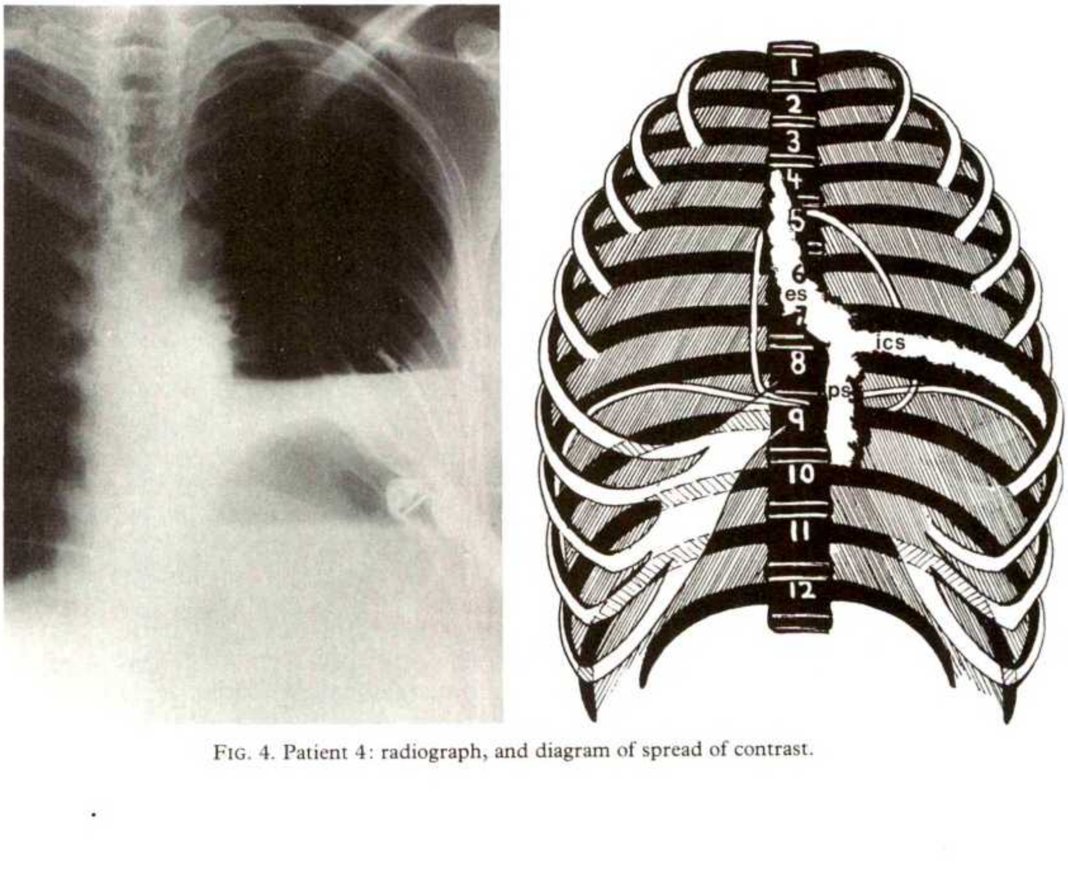

FIG. 4. Patient 4: radiograph, and diagram of spread of contrast.

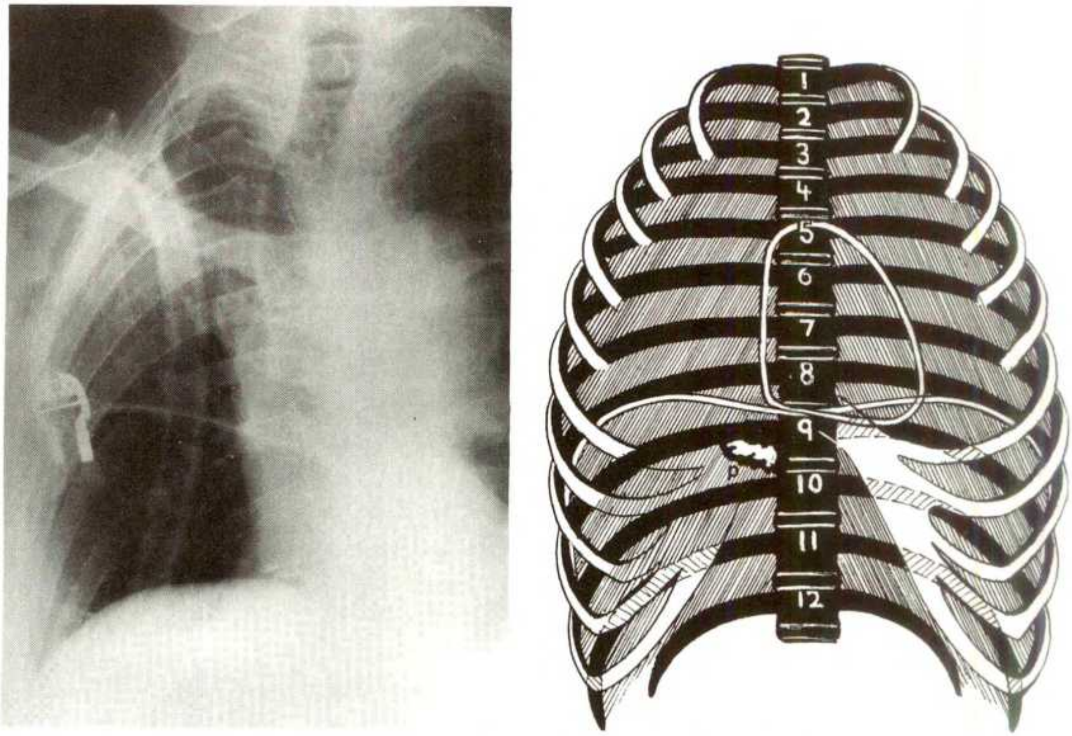

FIG. 5. Patient 5: radiograph, and diagram of spread of contrast.

graphy and angiography. It was used in this study in case, as indeed happened, it should inadvertently enter the extradural space. From the inception of the paravertebral injection technique (Kappis, 1919) it was recognized that a drug could enter the extradural space via the intervertebral foramena. However, neither with large volumes (up to 30 ml of bupivacaine) nor with continuous infusions have we found clinical evidence of contralateral neurological blockade, in more than 30 patients. A more recent case report (Middaugh et al., 1985), in which radioactive technetium was used as a tracer, has reconfirmed that local anaesthetic solution can reach the extradural space even when injected to the intercostal space, and there are several reports, similar to that of Otto and Wall (1976) of total spinal anaesthesia associated with intercostal nerve blockade.

Apart from the entry of drug to the extradural space, there is some argument as to the mechanism of overlapping analgesia achieved by the injection of local anaesthetic to an intercostal groove. Nunn and Slavin (1980) found in cadavers that India ink, in addition to passing paravertebrally, spread into adjacent intercostal spaces through a subpleural space anterior to and medial to the angle of the rib. This route may have been demonstrated radiologically in patient No. 2 of this study. A study in volunteers (Crossley and Hosie, 1987) using the contrast lopamidol has confirmed this mode of spread of an agent. However, Moore (1981) did not find this route in cadaver studies and thought that spread of effect was caused by medial movement of drug along the costal groove and that cephalad and caudad movement only occurred at and from the paravertebral space. We found that injection of contrast medium through a millipore filter and catheter is difficult, and at *in vitro* testing, contrast exits through the narrow bore catheter only drop by drop when injected from a 10-ml syringe. In order to achieve the distribution of contrast into the "potential" spaces found in our study, the tissue plane to which it was injected is likely to be of low resistance, with distal dispersal dependent, in part, on gravity. This view would tend to support that which suggests that spread of effect to other intercostal nerves is via the paravertebral space, spread along the route demonstrated by Nunn and Slavin (1980) perhaps being a phenomenon dependent on pressure of injection, on large injectate volume (Crossley and Hosie, 1987) and, as suggested by Moore (1981), on liquid consistency.

There is also some debate about the movement of drug from the paravertebral space. McIntosh and Mushin (1947) were quite adamant that spread to an ipsilateral space was only via the extradural space, each paravertebral space being virtually sealed anteriorly, posteriorly, above and below with access or egress only from the adjacent intercostal space and intervertebral foramen. Moore, Bush and Scurlock (1980), however, have shown that spread is across the heads of the ribs along the vertebral bodies. Most of these x-ray studies suggest that this may be the usual mode of spread of local anaesthetic. Where there is extensive caudad and cephalad movement, contrast gives a picture with a smooth paramedian border rather than anything that is lipped and suggestive of spread into intervertebral foramina. This suggests that, for clinical purposes, in many patients the paravertebral spaces are in continuity above and below. Nevertheless, patient No. 4 demonstrates graphically that the extradural route is occasionally of relevance. It is of interest to note that there was a fractured rib adjacent to the point where contrast appears to have entered the extradural space. It may be coincidence, but it is possible that the cephalad spread of contrast along the usual paravertebral route has been hindered by the trauma associated with the fracture.

Several reasons, not least demonstration of the movement of contrast close to the neuraxis, have meant that the series sample has had to be kept small. Thus it cannot be stated with any certainty that these patients are representative of the usual or likely modes of spread of drug injected to the paravertebral space. However, other clinical evidence for widespread, ipsilateral analgesia from a single injection to a thoracic paravertebral space is now substantive. One of our series had evidence of blockade in six dermatomes. McKnight and Marshall (1984) reported a patient with fractured ribs in whom contrast spread from the 3rd to the 12th thoracic dermatomes and the series of Eason and Wyatt (1979) contained similar examples. These latter authors achieved certainty of extensive blockade by using a two-catheter technique. Some of these x-ray studies confirm our own view that widespread analgesia beyond the confines of individual paravertebral spaces and the contiguous intercostal space can be obtained using large volumes of local anaesthetic and sitting patients upright at the time of injection at the upper part of the zone for which analgesia is intended.

There are several advantages to using the paravertebral route to intercostal nerves, besides widespread unilateral analgesia. The posterior primary ramus of the intercostal nerve branches from the main trunk within the paravertebral space. It supplies the posterior ligaments, posterior spinal muscles and overlying skin and, since these are often traumatized at thoracotomy, blockade of their nerve supply is worthwhile (Eason and Wyatt, 1979). The sympathetic chain lies within the space and unilateral sympathetic blockade is probably a useful adjunct as local vasodilatation can be obtained without the disabling hypotension so often found when an extradural technique is used (Conacher et al., 1983).

However, two possible complications remain, both of which have been illustrated in this study. Contrast has clearly been shown to enter the extradural space under some as yet undefined circumstances with the potential for severe hypotension as an accompaniment of widespread bilateral blockade. Second, puncture of the pleura is possible, so that in the undrained chest it has to be borne in mind that a paravertebral injection may initiate the development of a pneumothorax.

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CONTINUOUS INTERCOSTAL BLOCKADE AFTER CARDIAC SURGERY

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Intercostal nerve blockade improves pulmonary function after thoracic and upper abdominal surgery (Bridenbaugh et al., 1972; Bridenbaugh et al., 1973): impairment of gas exchange and the decrease in postoperative vital capacity are lessened. Local anaesthetic and radiopaque material injected to the extrapleural space spread up and down the chest wall (Nunn and Slavin, 1980) and several intercostal nerves can be blocked by a single injection of an appropriate volume of local anaesthetic. By extending this technique by inserting a catheter to the extrapleural space, one can provide continuous analgesia for several days with repeated injections of local anaesthetic through the catheter (O'Kelly and Garry, 1981; Murphy, 1983).

After cardiac surgery, lung volumes are usually reduced and gas exchange is impaired (Kaplan, 1979). Although most patients improve in the first few days after surgery, a significant number develop atelectasis and postoperative chest infection. In this institution, patients undergoing cardiac surgery usually receive moderate-dose opioid anaesthesia followed by artificial ventilation for 12–18 h with repeated i.v. opioid injections for analgesia after surgery.

Opioid drugs depress respiration, inhibit coughing and provide intermittent analgesia which is not particularly effective for the incident pain of coughing. To date there has been no controlled trial of continuous intercostal block for postoperative analgesia. Therefore, we have studied the quality of analgesia, pulmonary function and complications in patients after cardiac surgery using this technique and compared the results with those obtained in association with i.v. opioid analgesia.

SUMMARY

The provision of analgesia using continuous bilateral intercostal blockade was compared with that provided by conventional i.v. narcotics for the first 48 h after cardiac surgery. The subjective quality of analgesia was significantly superior with the regional technique. However, pulmonary function tests, gas exchange, lung volume, and radiological and clinical evidence of pulmonary complications were not improved. The failure to reduce morbidity and the potential for complications such as pneumothorax, makes it difficult to recommend the regional analgesia technique in this situation.

PATIENTS AND METHODS

The approval of the Human Experimentation Committee of Memorial University of Newfoundland, and the informed consent of each patient, was obtained. Patients undergoing elective cardiac surgery were allocated randomly with a random numbers table to receive either continuous intercostal analgesia or conventional i.v. opioid analgesia in the postoperative period. Smoking history, presence of chronic obstructive pulmon-

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ary disease, type of surgery, ventricular function and β-adrenoceptor blocking therapy were noted.

After premedication with papaveretum and hyoscine, anaesthesia was induced with fentanyl 5–7 $\mu g\ kg^{-1}$ and diazepam 0.1–0.2 $mg\ kg^{-1}$. Pancuronium 0.15 $mg\ kg^{-1}$ was given. Maintenance of anaesthesia was with nitrous oxide, enflurane or isoflurane, plus further increments of fentanyl and diazepam at the discretion of the anaesthetist. Perioperative fluids were administered according to the usual anaesthesia and ICU policies.

Bilateral intercostal catheters were placed in 20 patients at the end of surgery (Baxter, Flynn and Jennings, 1984). Analgesia was achieved by the injection of 20 ml of 0.25% plain bupivacaine (Marcaine, Winthrop Laboratories) through each catheter 6 hourly as required for the first 36 h after surgery. If analgesia was inadequate 30 min after the bupivacaine, morphine 2–5 mg i.v. was administered, the position of the catheters reassessed and further bupivacaine administration considered.

The other 20 patients had catheters taped to the skin to blind radiological and clinical assessment, and received i.v. morphine 2–5 mg as required for analgesia. Both groups received diazepam for anxiolysis at the discretion of the nursing staff, and after 48 h codeine by mouth, or opioids i.m. as required.

Blood-gas analysis, vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and inspiratory force were measured before operation, after weaning to 5 cm H_2O CPAP before extubation, after extubation on day 1, and on days 2, 3, and 5 after surgery.

Pulmonary function tests were all performed by the same technician and each recorded value is a mean of three manoeuvres. All the measurements were performed when the patient was comfortable, usually about 30 min after receiving the relevant "analgesic".

All chest radiographs were taken with the same radiological technique at full inspiration and in the same position (sitting, apart from the immediate postoperative film which was taken with the patient supine). The films were all assessed by the same radiologist. Planimetry was performed on the right lung to obtain an index of change in lung volume (Harris, Pratt and Kilburn, 1971) and the lung areas (volumes) were expressed as a percentage of the preoperative maximal inspiratory lung area (vital capacity). (The preoperative normal expiratory film shows the area at functional residual capacity (FRC) and the postoperative inspiratory films (VC) can be compared with these.)

A scoring system was used to quantify the amount of atelectasis: 1 = subsegmental atelectasis in one lobe; 2 = subsegmental atelectasis in more than one lobe; 3 = segmental atelectasis; 4 = lobar atelectasis; 5 = whole lung atelectasis.

Subjective quality of analgesia was recorded using a scale from 0 to 3 (no pain, mild, moderate and severe pain).

Chest complications were assessed clinically by auscultation, presence of pyrexia and quality of sputum, and were noted daily (score 1 = presence, 0 = absence of clinical signs). In all cases observers were blind as to the analgesic regimen being used.

Alveolar–arterial oxygen gradient ($PA_{O_2} - Pa_{O_2}$) was calculated from the alveolar gas equation:

$$PA_{O_2} = PI_{O_2} - \frac{Pa_{CO_2}}{R}.$$

Statistical analysis was performed using Student's t test (($PA_{O_2} - Pa_{O_2}$), FVC, inspiratory force and lung area), and Mann–Whitney U test (morphine dose, diazepam dose, pain score, chest signs and atelectasis score).

RESULTS

The two groups of 20 patients did not differ significantly with respect to sex, type of operation, ventricular function, intraoperative drugs (table I), and preoperative pulmonary function

TABLE I. *Demographic data*

	Intercostal analgesia	I.v. narcotics
Sex (M/F)	19/1	16/4
Surgery		
Coronary bypass graft (CABG)	17	15
Valve replacement	1	2
CABG + valve	2	3
Ventricular function		
Grade II	12	12
Grade III	5	5
Grade IV	3	3
Age (yr) (mean + SD)	55.0 + 7.4	55.0 + 9.1
Weight (kg) (mean + SD)	76.5 + 12.1	74.0 + 12.4
Intraoperative fentanyl ($\mu g\ kg^{-1}$ + SD)	9.8 + 1.9	10.1 + 1.5
Intraoperative diazepam ($mg\ kg^{-1}$ + SD)	0.45 + 0.08	0.43 + 0.10

TABLE II. *Pulmonary function tests and complications (mean+SD).* *P < 0.05

	Intercostal analgesia	I.v. analgesia
$(P\text{A}_{O_2}-Pa_{O_2})$ (kPa)		
Before op.	3.3+0.9	3.5+1.3
After op.		
Day 1	16.5+5.3	16.7+4.8
2	15.9+5.5	16.7+3.2
3	10.8+6.7	10.0+4.1
5	4.5+1.6	8.3+6.8
FVC (litre)		
Before op.	3.71+0.51	3.76+0.63
After op.		
Day 1	1.27+0.58	1.45+0.41
2	1.12+0.33	1.29+0.54
3	1.39+0.56	1.57+0.40
5	1.83+0.54	2.04+0.57
Inspiratory force (mm Hg)		
Before op.	118+39	116+41
After op.		
Day 1	79+43	73+43
2	88+48	89+40
3	104+50	95+41
5	125+42	115+41
Chest signs score (see text)		
Day 1	0.25+0.44	0.70+0.47*
2	0.35+0.48	0.60+0.50
3	0.40+0.50	0.50+0.51
5	0.10+0.31	0.20+0.41
Atelectasis score (see text)		
Day 1	0.55+0.94	0.20+0.41
2	1.1+0.91	1.15+0.99
3	1.05+0.83	1.35+1.23
5	1.05+0.89	1.1+0.97
Right lung area (% of pre-operative full inspiration)		
Pre-op. expiration	77+10	76+13
Post-extubation	77+10	80+11
Day 2 insp.	77+9	76+8
3 insp.	79+26	79+15
5 insp.	83+12	85+6

TABLE III. *Pain score, analgesia and anxiolytic requirements.* *P < 0.05; **P < 0.01

	Intercostal analgesia	I.v. analgesia
Bupivacaine injections (mean+range)		
Day 1	2.2 (1–4)	0
2	2.35 (1–4)	0
Morphine (mg) (mean+SD)		
Day 1	5.1+5.4	15.2+10.0**
2	3.8+6.2	9.7+6.8**
3	2.3+5.3	3.1+4.6
Diazepam (mg) (mean+SD)		
Day 1	10.3+9.0	15.8+6.6
2	1.8+4.0	6.7+6.4
Pain scores (mean+SD)		
Day 1	0.75+0.79	1.45+0.76**
2	0.70+0.57	1.15+0.49*
3	0.45+0.51	0.95+0.49
5	0 0	0.45+0.51*

($(P\text{A}_{O_2}-Pa_{O_2})$, FVC, and inspiratory force) (table II).

Patients receiving intercostal analgesia recorded significantly lower pain scores throughout the period of study; they also required less i.v. opioid analgesia and anxiolytic medication (table III). There was great variation in the duration of analgesia after each injection of bupivacaine, with a mean requirement of 2.2 (day 1) or 2.35 (day 2) injections per 24 h, but a range of 1–4 injections on each day.

Pulmonary function tests revealed similar changes in both groups (table II). There was a four-fold increase in $(P\text{A}_{O_2}-Pa_{O_2})$ on days 1 and 2 compared with before surgery, but no significant difference between the two groups except on day 5. FVC was reduced to about 30% of its preoperative values in both groups on days 1 and 2, with a slow recovery to 50–60% of preoperative values by day 5. Inspiratory force was reduced to about 65% of the preoperative value on day 1 in both groups, slowly recovering to normal by day 5.

Examination revealed fewer signs of atelectasis or chest infection in the intercostal analgesia group each day, but this was statistically significant only on day 1. Radiological assessment also failed to show any significant difference between the two groups in atelectasis scores. Planimetry indicated that, after surgery, the lung volumes were reduced so that maximal inspiration produced a lung area (volume) similar to that of the preoperative FRC; however, there was no difference between the two groups.

DISCUSSION

Thoracic and upper abdominal surgery impair pulmonary function markedly, but there are few published data relating specifically to the effect of median sternotomy and cardiac surgery on pulmonary function. The data reported here illustrate the profound effect of this type of surgery. Boysen (1982) reported a 57% incidence of atelectasis after cardiac surgery which was similar to the incidence (65%) in this study.

The beneficial effects of extradural analgesia with local anaesthetic drugs after upper abdominal surgery (Spence and Logan, 1975; Spence, Smith and Harris, 1976; Benhamou, Samii and Noviant, 1983) and thoracotomy (James et al., 1981) have been well documented. The perioperative use of anticoagulants limits the extradural aproach for many anaesthetists (Bromage, 1978) and the frequency of hypotensive problems (Griffiths, Diamond and Cameron, 1975; James et al., 1981) with extradural analgesia may make other regional techniques more attractive. Intercostal blockade has been found to be advantageous after thoracotomy (Faust and Nauss, 1976) and upper abdominal surgery (Bridenbaugh et al., 1972; Bridenbaugh et al., 1973). The demonstration of spread of solution beyond the site of injection (Nunn and Slavin, 1980) to produce a multiple segment blockade makes the continuous catheter technique attractive (O'Kelly and Garry, 1981; Murphy, 1983). Moreover, multiple segment blockade with 0.25% bupivacaine has only minimal effect on chest wall mechanics and lung volumes (Jakobsen et al., 1980). It was, therefore, interesting to assess this new technique after cardiac surgery, since there is a profound effect on pulmonary function, and since the use of anticoagulants and potential cardiovascular instability may contraindicate extradural analgesia.

Intercostal analgesia was superior as assessed by the patients, as they required less i.v. analgesia and reported significantly better pain scores than controls. They also required less anxiolytic medication, a further indication of patient comfort. However, despite the superior analgesia, there was no discernible difference in the indices of pulmonary function assessed. A bilateral multiple segment blockade might be expected to have more effect on chest wall mechanics and lung volumes in these patients than in the healthy volunteers in Jakobsen's study, and this might negate any small advantage from the superior pain relief. Separation of quality of pain relief from pulmonary function was also found by Bonnet and colleagues (1984), using extradural morphine after upper abdominal surgery, and Wahba and coworkers (1972) after thoracic surgery, and suggests that the effect of pain is overshadowed by the more major effects of mechanical disruption of the chest wall, possible reflex diaphragmatic dysfunction, changes in respiratory pattern after opioid anaesthesia and so on. Similarly, there was no evident reduction of pulmonary complications whether assessed clinically or radiologically.

No complications occurred in this study, although there is clearly a potential for pneumothorax and local anaesthetic toxicity; we have reported previously a patient who developed a massive flank haematoma, presumably from laceration of an intercostal vessel (Baxter, Flynn and Jennings, 1984). The lack of beneficial effect on pulmonary function and complications with the intercostal technique is disappointing, and one is left to balance the improved patient comfort against the potential for complications (Moore, 1985). The former is, of course, a comment on the efficiency of the opioid analgesic technique as well as on the regional technique. It is possible that the opioid technique might be improved by the use of more frequent doses or an infusion; this might achieve the same patient comfort as the regional technique, without the inherent risks.

We find it difficult to recommend continuous intercostal blockade for analgesia after cardiac surgery and suggest that its efficiency in other situations should be subject to appropriate controlled study.

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ORAL INTUBATION *V.* NASAL INTUBATION IN ADULT CARDIAC SURGERY

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SUMMARY

Time for intubation, incidence of mechanical complications, occurrence of bacteraemia caused by intubation, and postoperative discomfort were assessed in relation to nasal and oral tracheal intubation in adult cardiac surgery. The time for placement of the tube was 2.5 times longer for nasal intubation. Nasal bleeding was observed in 45.3% of patients intubated through the nose. In patients in whom a naso–tracheal tube was passed, 9.4% (v. 2.3% of patients intubated via the mouth), exhibited positive blood cultures just after intubation; however, the difference was not significant. Postoperative discomfort was similar in both groups. It can be concluded that nasal tracheal intubation offers no advantage over oral tracheal intubation in adult cardiac surgery.

The technique of high dose fentanyl anaesthesia is common in adult cardiac surgery because of its minimal effects on haemodynamic variables. The counterpart of this technique is the prolonged postoperative ventilatory depression which requires the institution of artificial ventilation for several hours. It is generally considered that nasal tracheal tubes are tolerated better than oral in these circumstances, and this belief explains why, in about 50% of all the patients undergoing open heart surgery in France, the nasal route was used during anaesthesia and in the postoperative period (Depoix, Desmonts and Tiret, 1984). However, specific complications related to the nasal route have been reported: nasal bleeding and post-intubation nasal discomfort (Fletcher et al., 1984), a higher incidence of bacteraemia (Berry, Blankenbaker and Ball, 1973) and acute maxillary sinusitis (Arens, Lejeune and Webre, 1974; Gallagher and Civetta, 1976; Willats and Cochrane, 1985).

The aims of this prospective study were to compare oral and nasal intubation in adult cardiac surgery, using the following criteria: time to achieve intubation, incidence of mechanical complications, occurrence of bacteraemia following intubation, and the assessment of postoperative comfort.

PATIENTS AND METHODS

One hundred adult patients undergoing open heart surgery were randomly allocated to undergo tracheal intubation via the nasal (N) or oral (O) route; 97 reports were analysed, 44 from group O and 53 from group N. Exclusion criteria included: age under 15 yr, subjects having a specific contraindication to nasal intubation, patients from group N in whom nasal intubation could not be performed, requirement for intubation of more than 72 h. Indices analysed during the stay *in the operating theatre* were:

(1) Time to achieve intubation (interval of time from the last inflation through the facial mask and the placement of the tube in the trachea).

(2) Technical problems and mechanical complications: nasal bleeding, difficulties in passing the tube either through the nose or through the glottis, rupture of the cuff.

(3) Occurrence of bacteraemia—assessed by two venous blood cultures performed, initially, before induction of anaesthesia and, then, 5 min after tracheal intubation. No prophylactic antibiotics were administered before the study.

The indices taken into account in the *intensive care unit* were the occurrence of acute sinusitis and of pulmonary atelectasis requiring antibiotic

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treatment for 8 days following tracheal intubation, trauma to the nostrils, assessment of the comfort of the patient 3 days after operation (by an interview performed by the same anaesthetist) and the presence of dysphonia, dyspnoea, dysphagia, and pain in the nose.

Results are expressed as mean ± SD. Blood cultures were compared using Chi-square test and *t* test for unpaired data was used for other comparisons.

RESULTS

Both groups were similar in regard to age (45 ± 19 yr in group O *v*. 47 ± 17 yr in group N), type of cardiac disease, duration of intubation including the duration of surgery (35.8 ± 17.7 h in group O *v*. 40.7 ± 18.4 h in group N). As expected, the time for the placement of the tube into the trachea was significantly shorter for the oral than the nasal route: 26 ± 30 s *v*. 62 ± 41 s.

Nasal bleeding was observed in 45.3% of group N patients during heparinization. Progress of the tube through the glottis was considered difficult in 17% of patients in group N *v*. 6.8% in group O—but the difference was not significant. In 13.2% of the patients selected for the nasal route, intubation could not be performed and the oral route had to be used. All blood cultures were negative before intubation in every patient. More patients in group N exhibited positive cultures after intubation (9.4%); 2.3% of patients from group O had positive cultures. However, this difference was not significant. The bacteria isolated were those usually present in nose, mouth and throat (table I). Several bacteria were isolated from the same blood culture in three patients. Thirteen patients (six from group O and seven from group N) underwent radiological examination of the maxillary sinus before, and 8 days after, operation. Sinusitis was found in only one patient (group N). No difference regarding pulmonary infection was found between the two groups. With respect to immediate postoperative discomfort in the ICU, there was no difference between oral or nasal intubation. However, 29.4% of patients from group N complained of pain in the nose for several days after extubation.

TABLE I. *Bacteria isolated from blood*

Species	Number of patients	
	Group O	Group N
Streptococcus sanguis	0	1
Corynebacterium species	1	1
Coagulase-negative staphylococcus	1	3

DISCUSSION

The results do not indicate any advantage of the nasal route compared with the oral route for intubation in adult cardiac surgery. The time required for the placement of tube into the trachea was 2.5 times longer when the nasal route was used. This point could be clinically relevant in some critically ill cardiac patients. In addition, intubation via the nose could not be performed in 13.2% of patients. This finding is in agreement with the report of Fletcher and colleagues (1984), who observed that nasal intubation was impossible in 17.3% of patients. Trauma to the nasal mucosa predisposes to bleeding during heparinization, and the placement of the naso–tracheal tube at the beginning of the operation was questioned in the light of this possibility.

Although bacteraemia was more frequent after nasal intubation, the difference was not significant. It is possible that a larger study would demonstrate more significant differences. Entry of bacteria to the blood stream after intubation by either the oral or nasal route may be potentially deleterious, especially in patients with valvular heart diseases. The aetiology of the bacteraemia is thought to be related either to the trauma of nasal or pharyngeal mucosa or to the transfer of the normal flow of mucus of the nasopharynx into the trachea. The species of bacteria identified in this study, and in a previous study (Berry, Blankenbaker and Ball, 1973), indicate that the bacteraemia was caused by nasal flora (alpha-haemolytic streptococci, *Corynebacterium* species and coagulase-negative staphylococci). These organisms have been isolated in patients with heart disease as those which cause subacute bacterial endocarditis—a point which should be taken into account in cardiac surgery. From these findings, it could be recommended that prophylactic antibiotic therapy start before intubation in adult cardiac surgery. In contrast, postoperative maxillary sinusitis was uncommon in our patients, although only a few patients could be investigated radiologically. In addition, the incidence of postoperative pulmonary complications was not different between the two groups. In regard to the discomfort caused by prolonged intubation, no difference was found between the two routes when the patients were interviewed in the postoperative period. Postextubation nasal pain was frequent, since it was reported by about 30% of patients intubated via the nose. These results are in accordance with the study of Fletcher and colleagues (1984), in which the patients were reintubated via the nose at the end of operation.

We conclude that nasal tracheal intubation carries no advantage over oral tracheal intubation in adult cardiac surgery. The occurrence of bacteraemia is not uncommon and should lead to a recommendation that prophylactic antibiotic therapy be instituted before the induction of anaesthesia in surgical patients having vascular or cardiac prosthesis, and valvular heart disease.

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PULMONARY VENTILATION AND GAS EXCHANGE BEFORE AND AFTER CORRECTION OF CONGENITAL CARDIAC MALFORMATIONS

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Pulmonary hyperperfusion resulting from congenital heart malformations may result, among other things, in mechanical changes in lung tissue which decrease compliance and impair gas exchange (Wallgren, Geubelle and Koch, 1960; Griffin et al., 1972; Howlett, 1972). Eventually, these result in pulmonary hypertension associated with histological changes in the pulmonary arteries and arterioles, and in their reactivity (Heath and Edwards, 1958; Maron, Redwood and Hirschfield, 1973; Burrows and Rabinovitch, 1985). These changes, which result in an increase in ventilation and a higher work load in the awake patient, should be evaluated before open heart surgery, and monitored during the induction of anaesthesia and the preparation of the child before cardiopulmonary bypass.

In the period immediately after open heart surgery and cardiopulmonary bypass hypothermia and fluid imbalance may also affect pulmonary function, particularly when ventilation has already been compromised before surgery. These physiological disturbances could be different in children with cyanotic cardiac malformations, presenting with hypoperfusion of the lungs, compared with in children with acyanotic anomalies in whom there is hyperperfusion of the lungs. In the present study pulmonary ventilation and gas exchange were evaluated before and after open heart surgery in 16 children.

SUMMARY

Sixteen children with congenital cardiac malformations were divided into cyanotic ($n = 9$) *and acyanotic* ($n = 7$) *groups, and pulmonary ventilation and gas exchange were assessed before surgery, after sternotomy, just after the completion of cardiopulmonary bypass (CPB), 30 min after CPB and after closure of sternostomy before transfer to ICU. Most patients in the cyanotic group had oligaemic, while all in the acyanotic group had overperfused, lungs before surgery. Total compliance was similar in the two groups. Alveolar ventilation was higher and the physiological deadspace to tidal volume ratio* (V_D/V_T) *lower in the acyanotic group compared with the cyanotic group* ($P < 0.05$) *before surgery. In the cyanotic group the preoperative large difference between arterial* (Pa_{CO_2}) *and end-tidal* ($P_{E'CO_2}$) *carbon dioxide tension was smaller immediately after CPB and remained so after closure of the sternum. In the acyanotic children the small arterial to end-tidal carbon dioxide difference before CPB had increased just after and 30 min after CPB, and* V_D/V_T *was significantly increased* ($P < 0.05$) *just after CPB. After closure of the sternum the arterial to end-tidal carbon dioxide difference and the* V_D/V_T *ratio had returned to baseline. The arterial to end-tidal carbon dioxide difference is a good indicator of ventilatory efficiency after open heart surgery.*

PATIENTS AND METHODS

Minute ventilation ($\dot{V}_E$), tidal volume (V_T), tracheal peak (P_{peak}) and pause (P_{pause}) pressures, end-tidal carbon dioxide tension ($P_{E'CO_2}$), the fraction of carbon dioxide in exhaled gas ($F_{E_{CO_2}}$) and arterial blood-gas tensions were measured

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TABLE I. *Patient characteristics. VSD = Ventricular septal defect; ASD = atrial septal defect; PDA = persistent ductus arteriosus*

Patient No.	Age (yr/m/d)	Body wt (kg)	Hb (g dl^{-1})	Hct (%)	Diagnosis	Operation	Duration of bypass (min)
Cyanotic							
1	4/2/0	15.7	17.7	60.2	Tricuspid atresia; pulm. stenosis; VSD; ASD	Fontan's procedure	108
2	0/3/18	5.8	16.3	52.9	Transposition of great arteries; PDA	Senning's procedure	86
3	6/3/0	16.4	14.7	47	Fallot, interrupted pulm. artery; previous Blalock–Taussig shunt	Correction	93
4	3/6/21	10.3	16.2	55.3	VSD; pulmonary stenosis; right-to-left shunt	Correction	189
5	2/2/2	10.5	16.3	53.1	Tetralogy of Fallot	Correction	66
6	0/7/0	7.2	19.0	58.8	Transposition of great arteries	Senning's procedure	98
7	0/3/0	4.4	15.9	46.9	Total anomalous venous drainage; TAVD	Correction	63
8	0/11/17	6.9	14.5	46.8	Tetralogy of Fallot	Correction	85
9	5/6/23	14.3	16.3	48.7	Pulmonary atresia; VSD; previous Blalock–Taussig shunt	Conduit closure VSD	137
Acyanotic							
10	2/2/0	12.9	12.9	40.3	VSD; slight infundibular stenosis	Closure; infundibular resection	67
11	0/8/27	5.2	11.0	33.7	VSD	Closure	62
12	0/4/0	4.2	10.4	32.0	VSD	Closure	68
13	4/0/19	14.9	13.9	41	Fallot; good palliation from previous Blalock–Taussig shunt	Correction	68
14	2/3/1	8.2	12.6	42	Acyanotic Fallot	Correction	156
15	5/0/16	16.9	12.5	37.8	Atrio–ventricular canal; Down's Syndrome	Correction	74
16	0/1/13	3.1	11.9	36.3	Transposition of great arteries	Senning's procedure	95

before and after cardiopulmonary bypass (CPB) in 16 children with congenital heart malformations subjected to open heart surgery for total correction or palliation of their cardiac anomaly. Carbon dioxide output ($\dot{V}\text{CO}_2$), alveolar ventilation ($\dot{V}\text{A}$), physiological deadspace volume ($V\text{D}$), $V\text{D}/V\text{T}$ ratios, arterial-to-end-tidal carbon dioxide differences ($Pa_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}$) and total compliance ($C^{\text{tot}}$) were calculated. The study was approved by the Hospital Ethical Committee.

Based on physical examination and cardiac catheterization, and on the results of chest x-ray, echocardiography, haemoglobin concentration (Hb) and haematocrit (Hct), the children were divided into two groups. The cyanotic group consisted of nine patients ranging in age from 3 months to 6 yr and with body weights ranging from 4.4 to 15.7 kg. All had evidence of hypoxaemia with high haemoglobin (Hb) concentrations and haematocrit values above the normal range ($\text{Hct} > 45\%$) (table I). Seven patients were acyanotic and ranged in age from 1 month to 5 yr, and weighed between 3.1 and 16.9 kg. These children had either normal or overperfused lungs, and normal Hb concentrations and Hct ($< 45\%$) values. Further patient data are given in table I.

All patients were fasted for at least 4–5 h before surgery. Children less than 10 kg were premedicated with atropine 0.2–0.3 mg i.m. only. Children between 10 and 15 kg received pethidine compound 0.07 ml kg^{-1} i.m. (1 ml contains: pethidine 25 mg, chlorpromazine 6.25 mg and promethazine 6.25 mg). Those heavier than 15 kg were premedicated with papaveretum 0.4 mg kg^{-1} and hyoscine 0.008 mg kg^{-1} i.m.

Anaesthesia was induced with cyclopropane in oxygen ($F\text{I}_{O_2}$ 0.5) and intubation of the trachea was facilitated by the administration of suxamethonium 1–1.5 mg kg^{-1}. Anaesthesia was maintained with 0.25–0.50% halothane in oxygen–nitrous oxide ($F\text{I}_{O_2}$ 0.5) and fentanyl 0.003–0.01 mg kg^{-1}. After the insertion of a radial artery cannula, and central venous catheters (via the internal jugular vein), the lungs were ventilated mechanically (Engström 2000 ventilator) at respiratory rates between 20 and 30 b.p.m., and with an I:E ratio of 1:2. Tubocurarine 0.4 mg kg^{-1} was administered to provide neuromuscular blockade.

A pneumotachograph (Fleisch No. 0) and an in-line capnometer (Hewlett–Packard, 14360 A) were placed in the patient deadspace. Airway pressure was measured at the tracheal tube connection with a Druck pressure transducer (PDCR-75). $\dot{V}\text{E}$ was measured by electrical integration of the flow signal from the heated pneumotachograph with a differential pressure transducer (Validyne MP 45-1-871; range ±2 cm H_2O). Flow, volume, end-tidal carbon dioxide and pressure signals were recorded on an ink jet recorder (Siemens Elema, EM 81). The deadspace of the system was 8 ml and its resistence 1.4 kPa litre^{-1} s^{-1} at a flow rate of 10 litre min^{-1}. The pneumotachograph was linear for flows up to 18 litre min^{-1}. Flow and volume calibrations were carried out with an accurate pump, and the capnometer calibrated with carbon dioxide of known concentration within the measuring range. The carbon dioxide signal was corrected for the presence of nitrous oxide and for the oxygen concentration.

Expired gas passed to a dry gas meter (Standard gas meter, AB Nordgas, Stockholm, Sweden) and then to a three-way valve from which a timed collection of a measured volume of gas could be made into a Douglas bag over 5 min. The $F\text{E}_{CO_2}$ of this gas was determined.

Arterial and central venous pressures were measured with Hewlett–Packard 1290 pressure transducers and, together with the ECG, recorded continuously on a Hewlett–Packard 775B monitoring system. Arterial blood (0.5 ml) was sampled in heparinized syringes and analysed within 3 min in a conventional blood-gas machine (Corning 168) which was calibrated daily.

Calculations

Body and room temperatures were measured regularly during measurements and $\dot{V}\text{E}$, $\dot{V}\text{A}$, $V\text{T}$ and $V\text{D}$ were corrected to body temperature and pressure saturated (BTPS). $\dot{V}\text{CO}_2$ values are presented at ambient temperature and pressure saturated (ATPS). The following formulae were used:

$$C^{\text{tot}}\ (\text{ml kPa}^{-1}) = \frac{V\text{T}}{P_{\text{pause}}}$$

$$\dot{V}\text{CO}_2\ (\text{ml min}^{-1}) = \text{gas collection } \dot{V}\text{E} \times F\text{E}_{CO_2}$$

$$\dot{V}\text{A} = \frac{\dot{V}\text{CO}_2 \times P_{\text{B}}}{P\text{a}_{CO_2}}$$

$$V\text{D} = \frac{\dot{V}\text{E} - \dot{V}\text{A}}{f}$$

where P_{B} indicates atmospheric pressure. In all patients body temperatures ranged between 36 and 37 °C during measurements.

Procedure

After the induction of anaesthesia, intubation of the trachea, arterial and venous cannulation and catheterization of the urinary bladder, mechanical ventilation was continued at an unchanged setting for at least 15 min before the first measurements—which were obtained *before the start of surgery*. In the middle of every 5-min period of gas collection, arterial blood (0.5 ml) was withdrawn for analysis. The next measurements were performed in a stable state of anaesthesia and surgery *after sternotomy* with the retractors in place. No blood, sodium bicarbonate or any vasoactive drug was given before CPB.

Extracorporeal circulation was carried out with a continuous flow at mean arterial pressures between 40 and 60 mm Hg and in no child was there any period of complete circulatory standstill. In most cases hypothermia to 18–20 °C was used. The heart–lung machine was primed with blood, mannitol and lactated Ringer's solution. A membrane oxygenator was used. The lungs were not ventilated during CPB. In no child was the bypass discontinued until the body temperature was 36 °C. Immediately after bypass, sodium bicarbonate and dopamine were infused in some patients. In all patients 100% oxygen was administered for the first 5 min after bypass.

Immediately after the termination of bypass—at a time when the circulation appeared stable—and when the venous and aortic cannulae had been withdrawn, further measurements were undertaken (at an $F\text{I}_{O_2}$ of 1.0). These were repeated 30 min later (*30 min after CPB*) when $F\text{I}_{O_2}$ was

TABLE II. *Mean values (±SEM) of mean arterial pressure and heart rate at the different stages of measurement in the cyanotic and acyanotic groups. CPB = cardiopulmonary by-pass*

	Mean arterial pressure (mm Hg)					Heart rate (beat min^{-1})				
	Before surgery	After sterno- tomy	Just after CPB	30 min after CPB	Sternum closed	Before surgery	After sterno- tomy	Just after CPB	30 min after CPB	Sternum closed
Cyanotic	77±5	79±7	60±4	72±4	69±3	134±6	128±8	135±11	148±7	152±9
Acyanotic	74±7	75±5	65±4	74±4	71±6	143±12	140±9	139±7	157±10	139±8

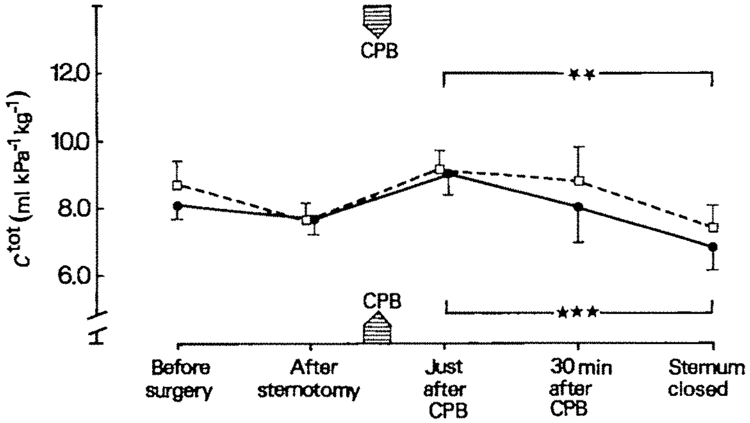

FIG. 1. Mean values (±SEM) of total compliance (C^{tot}) (ml kPa^{-1} kg^{-1}) at the various measuring stages. The cardiopulmonary bypass (CPB) is indicated. ●——● = Cyanotic group; □—□ = acyanotic group. $^{**}P < 0.01$ for the difference between C^{tot} just after CPB and after closure of the sternotomy in the acyanotic group; $^{***}P < 0.001$ for the corresponding difference in the cyanotic group.

decreased to 0.5–0.6 (care being taken not to measure at a time when sodium bicarbonate was being injected). In two children in the cyanotic group (Nos 4 and 9) dopamine 2.5–5 μg kg^{-1} min^{-1} was infused after CPB.

The final series of measurements was carried out when the *sternum* was *closed* with the patient still on the operating table.

Statistics

Mean values, standard deviation (SD) and standard error of the mean (SEM) were calculated. Variance analyses of distribution of data were performed and results were evaluated by unpaired and paired two-sided t tests. Probability values less than 0.05 were considered to indicate statistical significance.

RESULTS

At the various measuring stages there were no major changes in mean arterial pressure (MAP) or heart rate (table II). As expected, the lowest MAP values were found just after CPB with mean values (±SEM) of 60±4 mm Hg in the cyanotic and 65±4 mm Hg in the acyanotic group.

Mechanics of ventilation and arterial blood-gas tensions

Respiratory rates remained between 20 and 30 b.p.m. with a mean value (±SEM) in both groups of 25±1 b.p.m. P_{peak} and P_{pause} were also similar in the two groups. There were no statistically significant differences in C^{tot} between the cyanotic and acyanotic groups. The mean values (±SEM) of C^{tot} before surgery were 8.1±0.4 ml kPa^{-1} kg^{-1} in the cyanotic and 8.7±0.7 ml kPa^{-1} kg^{-1} in the acyanotic group. Corresponding values after CPB and the closure of the sternum were 6.8±0.6 ml kPa^{-1} kg^{-1} and 7.4±0.7 ml kPa^{-1} litre^{-1} kg^{-1}, respectively (fig. 1). The differences between C^{tot} before surgery and after the closure of the sternum were not statistically significant. In both groups C^{tot} was moderately increased just

TABLE III. *Mean values (±SEM) of inspiratory tracheal peak (P_{peak}) and pause (P_{pause}) pressures, minute ventilation ($\dot{V}E$), tidal volume (VT) and physiological deadspace volume (VD) at different stages of measurements in the cyanotic and acyanotic groups*

Measurement stages	P_{peak} (kPa)	P_{pause} (kPa)	$\dot{V}E$ (ml min^{-1} kg^{-1})	VT (ml kg^{-1})	VD (ml kg^{-1})
Cyanotic					
Before surgery	2.50±0.20	1.40±0.12	279±23	10.9±0.8	5.04±0.68
After sternotomy	2.44±0.16	1.44±0.12	286±21	11.1±0.8	5.16±0.82
Just after CPB	2.44±0.16	1.43±0.13	326±32	12.6±1.1	5.17±0.81
30 min after CPB	2.53±0.22	1.48±0.20	276±24	10.7±0.8	3.96±0.67
Sternum closed	2.71±0.26	1.63±0.19	265±29	10.5±0.9	3.74±0.67
Acyanotic					
Before surgery	2.61±0.28	1.46±0.21	312±49	12.3±1.4	3.80±0.85
After sternotomy	2.62±0.27	1.60±0.18	299±42	11.9±1.2	4.06±1.03
Just after CPB	2.49±0.19	1.49±0.18	333±47	13.4±1.4	6.86±1.35
30 min after CPB	2.61±0.27	1.54±0.25	324±53	13.1±1.9	6.15±1.77
Sternum closed	2.65±0.20	1.60±0.21	299±58	11.6±1.7	4.44±1.31

TABLE IV. *Mean values (±SEM) of arterial blood-gas tensions and end-tidal carbon dioxide tensions (PE'_{CO_2}) at different stages of measurement in the cyanotic and acyanotic groups. CPB = cardiopulmonary bypass. Statistically significant differences:* *$P < 0.05$, ***$P < 0.001$ *between measurements after sternotomy and just after CPB;* †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$ *between measurements after sternotomy and 30 min after CPB;* §$P < 0.05$, §§$P < 0.01$, §§§$P < 0.001$ *between measurements just after surgery and after closure of the sternotomy*

Measurement stages	pH	Pa_{CO_2} (kPa)	Pa_{O_2} (kPa)	HCO_3 (mmol $litre^{-1}$)	PE'_{CO_2} (kPa)
Cyanotic					
Before surgery	7.36±0.03	4.65±0.31	7.51±1.03	20.8±0.8	3.63±0.22
After sternotomy	7.34±0.03	4.47±0.22	8.02±1.19	19.3±1.1	3.64±0.24
	*		***		
Just after CPB	7.42±0.02	4.06±0.12	47.7±5.0	20.7±0.6	3.53±0.14
30 min after CPB	7.45±0.01††	4.18±0.20	22.8±2.6†††	22.7±1.0	3.70±0.18
Sternum closed	7.46±0.02§§	4.44±0.10§	21.0±2.1§§§	24.2±0.7	4.13±0.26§§
Acyanotic					
Before surgery	7.41±0.03	4.07±0.29	19.9±3.7	19.6±1.6	3.94±0.32
After sternotomy	7.39±0.02	4.12±0.26	14.0±2.0	19.3±1.3	4.10±0.34
		*	***		
Just after CPB	7.38±0.02	4.75±0.26	45.4±6.1	22.2±1.3	3.65±0.21
30 min after CPB	7.38±0.01	4.88±0.21†	24.3±5.0†	23.0±1.5	4.18±0.32
Sternum closed	7.42±0.02	4.58±0.29	25.7±6.4	23.1±2.0	4.40±0.33§

after bypass compared with before bypass, and these values decreased significantly ($P < 0.001$ in the cyanotic and $P < 0.01$ in the acyanotic group) after the closure of the sternum (fig. 1). $\dot{V}E$ and VT were slightly lower in the cyanotic group compared with in the acyanotic group, resulting in somewhat greater Pa_{CO_2} values before CPB in the former group. Just after, 30 min after CPB, and after the closure of the sternostomy, the volumes of ventilation were similar in the two groups (table III). Arterial oxygen tensions increased significantly in both groups just after CPB when an FI_{O_2} of 1.0 was used. After CPB the increase in oxygen tension remained throughout the procedure in the cyanotic group. In the acyanotic group there were no statistically significant differences in oxygen tension after the closure of the sternostomy when compared with values obtained before surgery when similar FI_{O_2} were used. In the cyanotic group pH increased (mean ± SEM) from 7.34±0.03 after sternotomy but before CPB, to 7.42±0.02 just after CPB ($P < 0.05$) and remained significantly higher than the value obtained before CPB (table IV).

Alveolar ventilation and VD/VT ratios

Before surgery the mean value (±SEM) of $\dot{V}A$ in the acyanotic group (212±28 ml min^{-1} kg^{-1}) was higher than that in the cyanotic group (149±21 ml min^{-1} kg^{-1}) ($P < 0.05$) (fig. 2). The difference between VD/VT ratios (mean ± SEM) in the two groups was also significant before

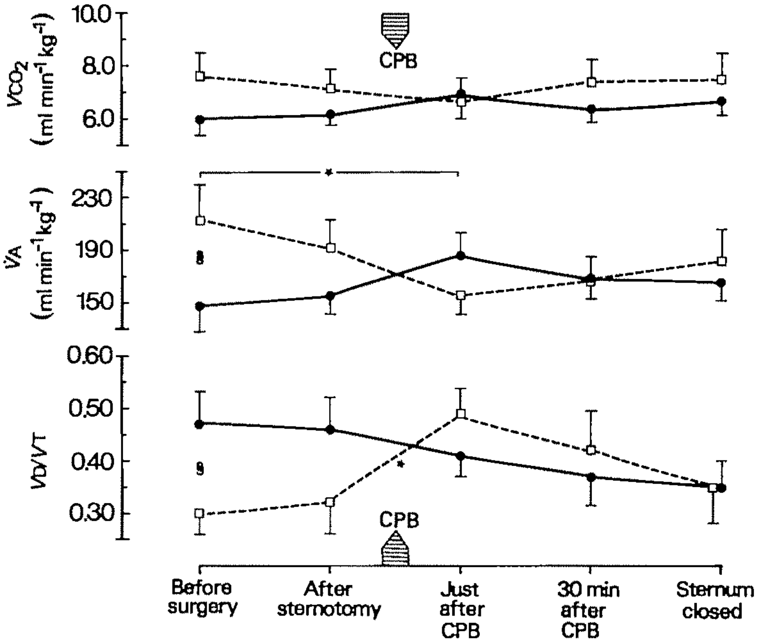

FIG. 2. Mean values (± SEM) of carbon dioxide output ($\dot{V}_{CO_2}$), alvleolar ventilation ($\dot{V}_A$) and V_D/V_T ratio in the cyanotic (●——●) and in the acyanotic (□---□) groups at the various stages of measurement. The cardiopulmonary bypass (CPB) is indicated. §$P < 0.05$ for the differences between the groups before surgery; *$P < 0.05$ for the differences in the acyanotic group between measurements before surgery and just after CPB for $\dot{V}_A$ and between measurements after sternotomy and just after CPB for V_D/V_T.

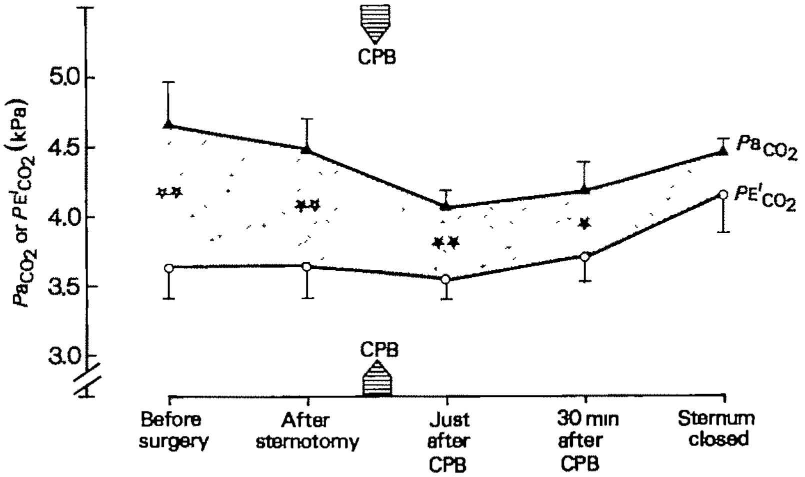

FIG. 3. The differences between mean values (± SEM) of arterial carbon dioxide tensions (Pa_{CO_2}) (▲) and end-tidal carbon dioxide tensions (PE'_{CO_2}) (○) in the cyanotic group. The shaded area indicates the difference between Pa_{CO_2} and PE'_{CO_2} at the various stages of measurement. *$P < 0.05$; **$P < 0.01$ for the differences between Pa_{CO_2} and PE'_{CO_2}. Note the narrowing gap between the two after closure of the sternum.

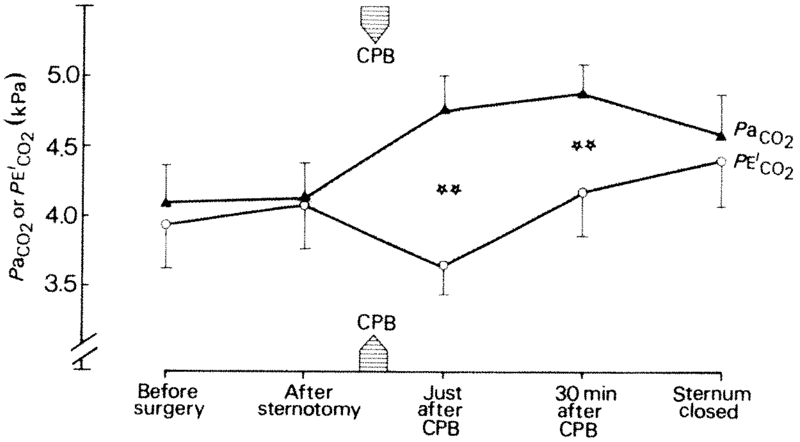

FIG. 4. The differences between mean values of arterial carbon dioxide tensions (Pa_{CO_2}) (▲) and end-tidal carbon dioxide tensions (PE'_{CO_2}) (○) in the acyanotic group. The shaded area indicates the difference between Pa_{CO_2} and PE'_{CO_2} at the various stages of measurement. $^{**}P < 0.01$ for the differences between Pa_{CO_2} and PE'_{CO_2}. Note the increased difference between the two just after and 30 min after CPB.

surgery with a lower value (0.30 ± 0.04) in the acyanotic group than in the cyanotic group (0.47 ± 0.06) ($P < 0.05$) (fig. 2). Sternotomy attenuated these differences and after CPB there were no differences in $\dot{V}_A$ and V_D/V_T between the two groups. In the acyanotic group V_D/V_T (mean ± SEM) increased, from 0.32 ± 0.06 after sternotomy but before CPB, to 0.49 ± 0.07 just after CPB ($P < 0.05$), and $\dot{V}_A$ decreased from 212 ± 28 ml min^{-1} kg^{-1} before surgery to 156 ± 13 ml min^{-1} kg^{-1} just after CPB ($P < 0.05$) (fig. 2).

Arterial to end-tidal carbon dioxide differences

Before surgery the difference between mean (± SEM) Pa_{CO_2} (4.65 ± 0.31 kPa) and PE'_{CO_2} (3.63 ± 0.22 kPa) was 22% ($P < 0.01$) in the cyanotic group, and this difference was also noted after sternotomy ($P < 0.01$). In the acyanotic group, however, the differences between Pa_{CO_2} and PE'_{CO_2} were small before CPB (fig. 3). Just after, and 30 min after, CPB ($Pa_{CO_2} - PE'_{CO_2}$) was still fairly high in the cyanotic group but decreased with time so that no difference existed after the closure of the sternum (fig. 4). Conversely, ($Pa_{CO_2} - PE'_{CO_2}$) in the acyanotic group increased just after ($P < 0.01$) and 30 min after ($P < 0.01$) CPB. This difference was no longer evident after the closure of the sternum (fig. 3).

DISCUSSION

Clinical evidence of cyanosis and laboratory investigations showing high haemoglobin concentrations and haematocrit (> 45%) values, together with subnormal arterial oxygen tensions referred the patients to the cyanotic group, which consisted of six patients with hypoperfused lungs. Two had transposition of the great arteries and one had total anomalous pulmonary venous drainage. The patients in the acyanotic group had all signs of a left-to-right shunt with overperfusion of the lungs. In spite of these differences in central circulation and arterial oxygenation, arterial carbon dioxide tensions were virtually the same in both groups throughout the study when similar ventilation volumes were used.

Since tracheal pause pressures were also similar in the two groups, no statistically significant changes of C^{tot} occurred between the groups at any of the measuring stages (fig. 1). C^{tot} was slightly lower than the total compliance found by Jonmarker (1985) in his study of lung mechanics in anaesthetized children subjected to cardiac surgery. However, the differences between the C^{tot} values presented in this study and those given by Jonmarker are not significant and might reflect differences in expiratory resistance. In Jonmarker's study there were a few patients in whom expiration was not complete, indicating a higher resistance than in the present series in which expiration was completed before the start of the next inspiration. C^{tot} values in this study were low compared with previously reported values (Lindahl, Okmian and Thomson, 1979) in normal children subjected to anaesthesia and intermittent positive pressure ventilation. This is in agreement with earlier reports from studies of awake spontaneously breathing children with cardiac malformations presenting with overperfused lungs (Wallgren, Geubelle and Koch, 1960). It was, however, unexpected in the cyanotic group in whom lung perfusion was predominantly low, since it has been shown by Howlett (1972) that lung compliance is normal in patients with congenital heart malformations and oligaemic lungs. The similarities of lung stiffness in the two groups in this series might be the result of a change in pulmonary blood volume secondary to anaesthesia and artificial ventilation in the acyanotic group, with pooling of blood in capacitance vessels. Such instant changes of pulmonary blood volume have been shown to improve lung compliance in children with congenital heart diseases and overperfusion of the lungs resulting from a left-to-right shunt (Howlett, 1972).

Sternotomy did not influence C^{tot} and, contrary to what would have been expected, C^{tot} was somewhat greater just after CPB than before. Furthermore, total compliance after the closure of the sternum was comparable to C^{tot} values before surgery—suggesting that no serious overhydration had occurred after CPB, since even moderate hypervolaemia is known to decrease total compliance (Lindahl, 1981).

Although Pa_{CO_2} values before the start of surgery were the same in both groups, the output of carbon dioxide was found to be somewhat lower in the cyanotic group, suggesting less efficient ventilation compared with the acyanotic group. However, this was more clearly demonstrated by the lower $\dot{V}_A$ and higher V_D/V_T ratio. This was most probably explained by the fact that most patients in the cyanotic group had hypoperfused lungs impairing gas exchange which also was reflected by the large $(Pa_{CO_2}-P_{E'CO_2})$ in this group.

After cardiopulmonary bypass oxygenation was normalized in the cyanotic group and this resulted in a significant increase in pH so that it remained normal during the rest of the operation. $(Pa_{CO_2}-P_{E'CO_2})$ was smaller, but the gap was still significant immediately after, and 30 min after, CPB. By the end of the operation, however, arterial and end-tidal carbon dioxide tensions were similar in the cyanotic group, indicating that an improvement in gas exchange had occurred. This was supported by a more efficient ventilation as judged from a somewhat higher alveolar ventilation and a lower V_D/V_T ratio found after closure of the sternum (fig. 2).

However, in the acyanotic group surgical correction and cardiopulmonary bypass resulted in a less efficient ventilation with a tendency to decreased alveolar ventilation and a significant increase in V_D/V_T ratio. This was also accompanied by a $(Pa_{CO_2}-P_{E'CO_2})$ that was much larger just after, and 30 min after, CPB than before CPB—when virtually no arterial-to-end-tidal carbon dioxide concentration difference existed in this group. This deterioration of gas exchange after CPB in children with overperfusion of the lungs could have been caused by the fluid overload that may occur after CPB. However, the same basic technique was used in the cyanotic group in whom the large $(Pa_{CO_2}-P_{E'CO_2})$ before surgery was not worsened just after CPB. Besides, C^{tot}, instead of being decreased after CPB—as would have been expected after a fluid overload—was increased somewhat—a finding which speaks against the fluid regimen used during CPB as a cause of impaired gas exchange in the acyanotic group after CPB.

Obviously, no clearcut explanation of the sudden change in gas exchange in the acyanotic group is readily apparent. As a result of the operation, lung perfusion and the filling of pulmonary arteries and arterioles was dramatically changed. This must have resulted in an altered pulmonary artery wall tension as well as in different working conditions for the hypertrophic arteries. The consequences could be an increased pulmonary artery contraction that decreased lung perfusion and increased the ventilation perfusion mismatch so that $(Pa_{CO_2}-P_{E'CO_2})$ became larger without changing total compliance. Unfortunately, pulmonary artery pressures were not followed in this study. However, although the background of the cause of events for the worsened gas exchange after CPB in patients with overperfused lungs before surgery is unknown, it recovered before the patients were transported to the ICU. The increased difference between the arterial-to-end-tidal carbon dioxide tension after CPB in patients with hyperperfused lungs could have the same explanation as the postoperative pulmonary hypertensive crisis described by Sumner (1985) which occurs particularly in children with hyperperfusion of the lungs subjected to open heart surgery for corrections of congenital malformations.

It is concluded that children with congenital cardiac malformations resulting in cyanosis have a less efficient ventilation and gas exchange before surgery with a large ($Pa_{CO_2} - P\text{E}'_{CO_2}$). This is improved immediately after surgical correction and cardiopulmonary bypass. In acyanotic patients with malformations presenting with overperfusion of the lung, ventilatory efficiency and gas exchange before surgery are good. Immediately after open heart surgery, however, these patients show impairment of ventilatory efficiency and gas exchange with an increased ($Pa_{CO_2} - P\text{E}'_{CO_2}$), which might be the result of a sudden change of the tone in pulmonary arteries. Careful monitoring of gas exchange immediately after cardiopulmonary bypass and in the postoperative period is advised in these patients.

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SINGLE-SHOT I.V. ANAESTHESIA FOR OUTPATIENT DENTAL SURGERY

Comparison of 2,6 Di-isopropyl Phenol and Methohexitone

M. R. LOGAN, J. E. DUGGAN, I. D. LEVACK AND A. A. SPENCE

SUMMARY

A single i.v. bolus dose of propofol 3 mg kg^{-1} was compared with methohexitone 2 mg kg^{-1} as the sole anaesthetic agent for simple dental extraction in outpatients. Induction of anaesthesia was smoother with propofol, with a lower incidence of excitatory phenomena. Pain on injection was a common complication of both drugs and related to the site of injection. The Leeds Psychomotor Tester was used to assess psychomotor performance during the recovery. Rate of recovery from anaesthesia was similar with both agents, and there was little residual impairment of psychomotor function 40 min after induction.

One outstanding feature of outpatient dental anaesthesia is the fact that many of the surgical procedures can be completed within the duration of anaesthesia provided by the induction agent. Following the procedure, it is desirable that recovery from anaesthesia be rapid and result in early ambulation and clearheadedness. Of the induction agents generally available, methohexitone has been the agent of choice (Whitwam, 1976). However, early studies on 2,6 di-isopropyl phenol (propofol) in Cremophor EL (Rutter et al., 1980; Wells, 1985), and more recently in an aqueous formulation (MacKenzie and Grant, 1985), have shown that the rate of recovery from anaesthesia was similar to that associated with methohexitone.

This study was designed to characterize the quality of anaesthesia and recovery, with special reference to psychomotor performance, associated with a single i.v. bolus dose of propofol in aqueous emulsion formulation (Diprivan), and to compare the results with those obtained with methohexitone (Brietal) given in the absence of other anaesthetic agents. Patients undergoing simple dental extraction(s) were studied.

PATIENTS AND METHODS

Forty healthy unpremedicated patients of either sex aged between 16 and 70 yr who were to have one or two teeth extracted under general anaesthesia were studied. None had received a sedative drug in the previous 3 days. Patients gave written informed consent and the study was approved by the hospital ethics committee. The patients were randomly allocated to receive either propofol ($n = 21$) or methohexitone ($n = 19$). The quality of anaesthesia and the characteristics of recovery were assessed by an independent observer under double-blind conditions.

Preoperative assessments

Psychomotor performance was assessed with the Leeds Psychomotor Tester. This is capable of measuring Critical Flicker Fusion Threshold (CFFT) and Choice Reaction Time (CRT). These tasks have been used widely to assess the central nervous system arousal and the sensori–motor impairment produced by psychoactive drugs (Hindmarch, 1980). Recently, they have been

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applied as tests of recovery from anaesthesia (MacKenzie and Grant, 1985). All assessments were made in the same quiet, uniformly lit, room and after a period of familiarization with the apparatus. Each subject was asked to use the index finger of the dominant hand when performing CRT and encouraged to respond as quickly as possible. At each assessment, CRT was taken as the mean of the last 25 response times out of a series of 30. Total Reaction Time (TRT) was determined as the time interval between the illumination of the signal light and the subject's finger reaching the correct choice button. The latency component of the CRT was taken as the time required for the finger to leave the resting button. The motor component was derived by subtracting the latency component from TRT. CFFT was performed at a foveal fixation of 1 m and taken as the mean of three ascending and descending frequency challenges.

Postural balance was assessed using a Wright–Codoc Ataxiameter (Wright, 1971). This device measures the integrated and summated antero–posterior sway (linear sway) in minutes of arc during a 1-min period. The test was performed without footwear and over two 1-min periods, the mean value being quoted in the results.

Subjective assessments of drowsiness, anxiety, balance and pain were made by 10-cm linear visual analogue scales (VAS).

Anaesthetic technique

A McKesson dental prop was positioned and anaesthesia induced with either 1% propofol 3 mg kg^{-1} or 1% methohexitone 2 mg kg^{-1} as a slow i.v. injection over 20 s to a peripheral vein. Dental extraction was performed as soon as anaesthesia had been induced. After the tooth (or teeth) was extracted the patient was turned to the semi-prone position and allowed to recover.

A second anaesthetist acted as an independent observer, recorded any side effects and assessed the overall quality of anaesthesia. During the injection the patient was asked "Is your arm comfortable?" and to describe any sensations at the site of injection. If they complained of pain it was assessed as mild, moderate or severe. The same dental surgeon, who was unaware of the agent injected, performed all the extractions and was asked to assess the surgical conditions as good, adequate or poor.

Assessment of recovery

During recovery from anaesthesia, the time intervals from induction until opening eyes on command, to correct recall of date of birth, and to sitting unaided were recorded. At intervals of 15 and 40 min after induction of anaesthesia, further measurements of CRT, CFFT, postural balance and VAS were made in sequence.

All patients were allowed to go home, accompanied, 1–2 h after induction and following inspection of the vein used for the injection.

Statistical methods of analysis were Wilcoxon Signed Rank, Wilcoxon Rank Sum Test, and Chi-squared test on appropriate data.

RESULTS

Forty patients participated in the study, 21 in the propofol group and 19 in the methohexitone group. There were no significant differences between the patients in either treatment group in terms of age, weight and sex distribution (table I).

Induction characteristics

Both agents were rated as equally acceptable by the observer and the dental surgeon (table II). However, minor complications on induction were common in both groups (table III). There was a high incidence of pain on injection with both drugs (propofol 33%; methohexitone 36%) which was rated mild or moderate in intensity. A cold painless sensation was experienced by a further five patients in the propofol group. Feelings on injection were closely related to the site of injection. Methohexitone caused pain on injection in seven of 11 patients in whom a dorsal hand vein was used, and in none of the eight patients in whom an antecubital vein was used ($P < 0.005$). Taking all of the sensations (pain and coldness) associated with the administration of propofol, 11 of 15 patients in whom a hand vein, and one of six patients in whom an antecubital vein was used experienced an unpleasant sensation. This difference just failed to reach statistical significance at the $P = 0.05$ level.

TABLE I. *Demographic data (mean ± SEM)*

	Propofol	Methohexitone
Age (yr)	25.3±2.0	28.2±2.7
Weight (kg)	61.3±2.0	66.4±3.1
Male/Female	4/17	6/13

TABLE II. *Assessment of quality of anaesthesia, recovery and operating conditions. Number of patients in each category. Mx = Methohexitone; Prop. = propofol*

	Observer				Dental surgeon			
	Induction		Recovery		Conditions		Duration	
	Mx	Prop.	Mx	Prop.	Mx	Prop.	Mx	Prop.
Good	19	16	16	15	19	18	17	17
Adequate	0	5	3	6	0	3	2	4
Poor	0	0	0	0	0	0	0	0

TABLE III. *Complications on induction and during anaesthesia. Number of patients. Between group comparison:* *P < *0.05,* **P < *0.01*

	Propofol	Methohexitone
Feelings on injection		
All	12	7
Pain	7	7
Other: coldness	5	0
hotness	0	2
Excitatory effects on induction (hypertonus, tremor and hiccup)	3	11**
Apnoea on induction (> 20 s)	3	5
Movement in response to extraction	8	4*
Total	26	27 ns

TABLE IV. *Recovery intervals from induction of anaesthesia (min) (mean ± SEM). Between group comparison:* *P < *0.05;* **P < *0.01*

	Propofol	Methohexitone
Eye opening	6.38±0.54*	4.26±0.52
Recall of date of birth	7.57±0.54**	5.7 ±0.54
Sitting unaided	10.62±0.53	9.42±0.69

There was a high incidence of excitatory phenomena on induction with methohexitone (57%); these were seen infrequently with propofol (14%) ($P < 0.01$).

In each patient the depth and duration of anaesthesia was adequate to permit completion of surgery. Minor limb movement in response to surgery was more common in the propofol group (38%), than in the methohexitone group (21%) ($P < 0.05$).

Apnoea of greater than 20 s was observed in three patients in the propofol and in five patients in the methohexitone groups (ns). All had resumed spontaneous ventilation by 40 s.

TABLE V. *Psychometric data and linear sway (mean ± SEM)*

	Propofol	Methohexitone
CFFT (Hz)		
Before op.	33.2±0.93	32.8±0.8
15 min	31.8±1.0	31.8±0.8
40 min	32.6±0.85	31.9±0.8
CRT TRT (ms)		
Before op.	630.3±20.6	603.1±29.4
15 min	734.7±42	730 ±18.9
40 min	634.5±24.3	633 ±21.7
CRT latency (ms)		
Before op.	401 ±15.4	381.2±10.9
15 min	489.9±28.2	457.1±22.7
40 min	419.4±15.4	398.6±14.0
CRT motor (ms)		
Before op.	224.5±11.2	221.9±19.4
15 min	244.7±16.7	271.4±18.9
40 min	214.5±12.5	235.5±12.8
Linear AP sway		
Before op.	27.6±2.5	26.8±2.5
15 min	32.3±2.9	38.3±4.5
40 min	26.6±2.3	27.5±3.21

Recovery characteristics

The time interval from induction to opening eyes on command ($P < 0.01$), recall of correct date of birth ($P < 0.02$) and sitting unaided (ns) were delayed in the propofol group (table IV). Fifteen minutes after induction all patients were able to walk unaided 15 m to the assessment room.

The results of the psychometric studies and linear sway are given in tables V and VI. There was no statistically significant difference between the propofol and methohexitone groups in these tests when assessed before operation, or at any time during recovery. Fifteen minutes after induction both agents caused prolongation of TRT, methohexitone by 21% and propofol by 17% of preoperative values. The latency component of TRT showed a similar prolongation in

TABLE VI. *Psychometric data and linear sway expressed as changes from preoperative values (mean ± SEM). Compared with preoperative values:* **$P < 0.05$; **$P < 0.02$; ***$P < 0.01$*

	Propofol	Methohexitone
CFFT (Hz)		
15 min	−1.48±0.5**	−0.74±0.26**
40 min	−0.6±0.5	−0.64±0.27*
TRT (ms)		
15 min	+104.5±31.7	127.4±34.0
40 min	+3.8±14.4	30.1±22.2
Latency (ms)		
15 min	+84.2±21.8**	75.9±23.3***
40 min	+13.7±11.4	19.2±14.2
Motor (ms)		
15 min	+20.3±12.0	51.5±20.3*
40 min	−10.0±12.0	12.7±14.8
Linear sway (minutes of arc)		
15 min	+3.98±2.24	+11.5±3.8***
40 min	−0.79±1.07	+1.18±2.7

each group, methohexitone 20% ($P < 0.02$) and propofol 22% ($P < 0.02$). The motor component of TRT increased significantly by 22% in the methohexitone group ($P < 0.05$), but the 9% increase in the propofol group failed to reach significance. By 40 min the CRT of both groups had virtually returned to control in respect of all mean values.

Linear sway increased with both drugs 15 min after induction, methohexitone by 43% and propofol 17%, but this only reached statistical significance in the methohexitone group ($P < 0.01$). At 40 min patients in both groups had recovered their preoperative abilities.

Both agents significantly depressed mean CFFT frequencies at the 15 min assessment (methohexitone 2.2%, $P < 0.02$; propofol 4.4%, $P < 0.02$). At 40 min mean CFFT frequency for both drugs remained depressed at 1.8%. This was statistically significant only for the methohexitone group ($P < 0.05$).

Patients' subjective assessments of "drowsiness", "anxiety", "steadiness" and "pain" are given in figure 1. At 15 min both agents caused the patient to feel more drowsy ($P < 0.01$), less steady ($P < 0.02$) and less anxious ($P < 0.01$). By 40 min the feelings of drowsiness and unsteadiness had returned to preoperative values. However, the methohexitone group rated themselves significantly steadier than did the propofol group by this time ($P < 0.05$). The decrease in anxiety at 15 min was still apparent at 40 min. Both groups showed a small increase in pain after extraction.

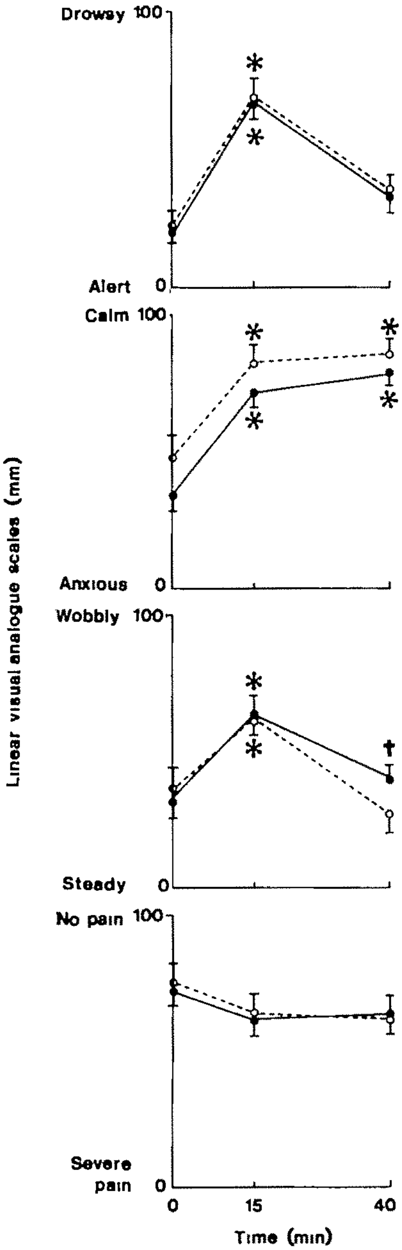

FIG. 1. Linear visual analogue scales: alert/drowsy; anxious/calm; steady/wobbly; severe pain/no pain. ●—● = Propofol; ○-----○ = methohexitone (mean values; bars represent standard error). Significant differences ($P < 0.05$): *compared with value before operation; †between groups.

DISCUSSION

Patients slept slightly longer after propofol than after methohexitone, but further recovery was rapid and comparable. Propofol appeared to cause less deterioration of motor function (motor component of CRT) and balance (linear sway) 15 min after induction. By 40 min there was little evidence of residual impairment of psychomotor performance with either drug, although preoperative psychomotor function could have been adversely affected by anxiety. These patients have often been refused treatment under local anaesthesia because of a morbid anxiety state.

We feel that the doses of each agent given in this study were comparable. The dose of methohexitone 2.0 mg kg^{-1} was that used in our normal clinical practice. Recent studies have indicated that propofol 2.5 mg kg^{-1} is a satisfactory dose for induction of anaesthesia followed by a standard inhalation technique (Cummings et al., 1984; Valanne and Korttila, 1985). In a pilot study we found propofol 2.5 mg kg^{-1} i.v. provided adequate anaesthesia in only eight of 10 unpremedicated patients undergoing dental extraction, as a result of the intense surgical stimulation occurring immediately after induction. The higher dose of propofol 3 mg kg^{-1} was chosen for the main study to provide a depth of anaesthesia equivalent to our clinical experiences with methohexitone. Even with the relatively large dose of propofol given in this study, there was a high incidence of minor limb movement in response to the extraction. Although this did not interfere with surgery, the effect of i.v. analgesic supplementation on propofol dosage requirement and side effects is worthy of further investigation in this clinical setting.

This study confirms the findings of previous studies (Rutter et al., 1980; Wells, 1985) that the incidence of pain on injection is high with both drugs when small distal veins are used, and that a clinically significant improvement can be obtained by using larger antecubital veins. Excitatory phenomena (hypertonus, tremor and hiccup), a recognized and potentially dangerous problem of induction with methohexitone (Dundee and Moore, 1961), were frequent in the methohexitone group and uncommon when propofol was administered.

In conclusion, the quality and rate of early recovery from single i.v. bolus doses of propofol 3 mg kg^{-1} and methohexitone 2 mg kg^{-1} were similar. The smoothness of induction and the lower incidence of excitatory phenomena with propofol would appear to be advantageous.

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HIGH- AND LOW-DOSE FENTANYL ANAESTHESIA: CIRCULATORY AND PLASMA CATECHOLAMINE RESPONSES DURING CHOLECYSTECTOMY

C. KLINGSTEDT, K. GIESECKE, B. HAMBERGER AND P.-O. JÄRNBERG

SUMMARY

The cardiovascular and neuroendocrine effects of a high-dose fentanyl anaesthesia (100 µg/kg body weight) were compared with those of a balanced type of fentanyl anaesthesia (5 µg kg^{-1}) during upper abdominal surgery. High-dose fentanyl anaesthesia prevented the increase in catecholamine concentrations and attenuated the circulatory response to surgical stress seen in the group anaesthetized with the balanced technique of anaesthesia.

High-dose (50–150 µg kg^{-1}) fentanyl anaesthesia is used widely in open-heart surgery (Stanley and Webster, 1978; Lunn et al., 1979) since it provides acceptable cardiovascular stability during anaesthesia and surgery (Stanley, Philbin and Coggins, 1979; Lappas et al., 1980). It has also been shown that this regimen decreases the usual neuroendocrine stress response associated with sternotomy (Stanley et al., 1980; Sebel et al., 1981)—although differences of opinion exist (Walsh et al., 1981; Zuric et al., 1982).

Plasma catecholamine concentrations have been measured during surgery by several groups, both during high-dose fentanyl anaesthesia (Stanley, Philbin and Coggins, 1979; Lappas et al., 1980; Sebel et al., 1981; Zuric et al., 1982) and during a standard neurolept anaesthesia using fentanyl 10 µg kg^{-1} (Tammisto et al., 1973; Balogh et al., 1979; Hamberger and Järnberg, 1983). Fentanyl 50–75 µg kg^{-1} has been shown to reduce the metabolic and hormonal changes occurring during abdominal surgery (Hall et al., 1978; Cooper et al., 1981; Haxholdt, Kehlet and Dyrberg, 1981). However, data on the stress response and plasma catecholamine concentrations when using fentanyl in doses of 100 µg kg^{-1} or more are lacking.

The purpose of this study was to compare the cardiovascular and neuroendocrine effects of high-dose (100 µg kg^{-1}) fentanyl anaesthesia with those of a balanced type of anaesthesia using fentanyl in a dose of 5 µg/kg body weight during upper abdominal surgery. This was accomplished by the use of a standardized surgical procedure and a catecholamine sampling scheme correlated with certain events during anaesthesia and surgery, thereby facilitating comparisons between the two different techniques of anaesthesia.

PATIENTS AND METHODS

Patients

Twelve patients, scheduled for routine cholecystectomy, were studied. They were randomly divided into two groups. Six patients received high-dose fentanyl (group 1); the remainder (group 2) received the balanced technique of fentanyl anaesthesia. All were healthy, except for their gallbladder disease. Preoperative ECG recordings and chest x-rays were normal. The patients were not on any continuous medication. The characteristics of the patients are summarized in table I.

The study was approved by the Ethical Committee of the Karolinska Institute, and informed consent was obtained from each patient.

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TABLE I. *Patient characteristics (mean ± SEM). Group 1 received high-dose fentanyl anaesthesia; group 2 a balanced anaesthetic technique.* * *Time from start of anaesthesia to end of operation*

	No.	Male/ Female	Age (yr)	Weight (kg)	Anaesthetic time (min)*
Group 1	6	1/5	47.3±4.1	58.5±3.4	100±16
Group 2	6	2/4	39.3±4.7	68.0±4.2	128±18

TABLE II. *Sampling times for plasma catecholamines*

(1) Before induction of anaesthesia, at least 15 min after completion of catheterization.
(2) 1 min after tracheal intubation.
(3) Immediately before skin incision after 15–30 min of anaesthesia.
(4) 1 min after skin incision.
(5) During surgical exploration of the gallbladder.
(6) After 10 min intermission of surgery.
(7) 5 min after the operation had been resumed.

No complications attributable to the study occurred.

Anaesthesia

The patients were premedicated with morphine 0.15 mg kg^{-1} given i.m. approximately 1 h before the induction of anaesthesia. All patients received atropine 0.5 mg and diazepam 0.1 mg kg^{-1} i.v. immediately before induction.

In group 1, anaesthesia was induced with fentanyl 100 μg kg^{-1}, given as a bolus over 2 min; no further fentanyl was given to this group. The induction of anaesthesia in group 2 consisted of i.v. thiopentone 4–5 mg kg^{-1} and fentanyl 5 μg kg^{-1}, followed by a continuous infusion of fentanyl 3 μg kg^{-1} h^{-1}.

Neuromuscular blockade was obtained in all patients with pancuronium 0.1 mg kg^{-1}. The lungs of all patients were mechanically ventilated with nitrous oxide in oxygen (2:1), to normocapnia—as confirmed by blood-gas analyses (ABL-2).

Arterial samples were drawn into heparinized tubes, stored on ice, and centrifuged within 1 h. The plasma was frozen and stored at −70 °C until analysis. One millilitre of plasma was then used for the assay. The catecholamines were separated by high pressure liquid chromatography and quantified by electrochemical detection (Hallman et al., 1978). The sensitivity of the method was ±0.1 nmol litre^{-1}. Total sampling blood loss was less than 150 ml, including blood sampling for other chemical analyses.

Procedure

A peripheral vein was cannulated and an infusion of lactated Ringer's solution commenced at 200 ml h^{-1}. The left radial artery was cannulated (20-gauge Teflon catheter) to permit measurement of arterial pressure (Kontron 128A monitor with a pressure transducer (Bentley)). Mean arterial pressure was obtained by electronic damping of the pressure signal. Heart rate was determined from the ECG.

Arterial samples for the measurement of catecholamine concentration were drawn as detailed in table II. Systolic arterial pressure (SAP) and heart rate (HR) were registered at these times. Blood lost was replaced with twice its volume of lactated Ringer's solution. No patient lost more than 500 ml of blood (including sampling).

Statistics

Statistical analyses consisted of calculations of mean value, standard deviation, and standard error of the mean (SEM). Student's t test for paired and unpaired data, with pooled estimates of variance, was used to compare data within and between the two groups, respectively. $P < 0.05$ was considered to indicate a significant difference.

RESULTS

Unless otherwise stated the values given below are the averages in each group for the different sampling points.

Plasma adrenaline concentration (table III)

Adrenaline concentrations were similar in both groups initially (0.5 nmol litre^{-1} in group 2 and 0.3 nmol litre^{-1} in group 1). In both groups, these concentrations decreased significantly to <0.1 nmol litre^{-1} after the induction of anaesthesia. In group 1 this value persisted throughout the entire operation.

In group 2 the adrenaline concentration increased significantly during periods associated with the surgical exploration of the gallbladder: concentrations of 1.4, 0.6 and 0.9 nmol litre^{-1} were found during surgery, after 10 min of interruption, and when surgery was resumed; all were significantly greater than those recorded in

TABLE III. *Plasma adrenaline and noradrenaline concentrations (mean ± SEM). Significant differences: *From (1) group 1 (P < 0.05); †from (1) group 2 (P < 0.05); **from (4) group 1 (P < 0.01); ††from (4) group 2 (P < 0.01); ‡from (4) group 1 (P < 0.05); §from (4) group 2 (P < 0.05); ¶between groups 1 and 2 (P < 0.05)*

	Adrenaline		Noradrenaline	
Sample	Group 2	Group 1	Group 2	Group 1
(1)	0.5±0.3	0.3±0.1	1.4±0.4	1.5±0.3
(2)	<0.1	<0.1*	1.0±0.3	1.0±0.1*
(3)	<0.1	<0.1*	0.9±0.2†	0.8±0.1*
(4)	<0.1	<0.1*	0.8±0.3†	0.8±0.1*
(5)	1.4±0.6§	<0.1*¶	1.5±0.4††	1.5±0.2**
(6)	0.6±0.2§	<0.1*¶	1.6±0.3††	1.1±0.2
(7)	0.9±0.4§	<0.1*¶	1.5±0.3§	1.3±0.1‡

group 1 ($P < 0.05$). There were no increases in adrenaline concentration during intubation in either group.

Plasma noradrenaline concentration (table III)

The initial noradrenaline concentrations were 1.4 nmol litre^{-1} in group 2 and 1.5 nmol litre^{-1} in group 1. The same pattern was evident in both groups, with an initial decrease after the induction of anaesthesia. During surgical stimulation noradrenaline concentrations increased to their preinduction values.

Heart rate, systolic arterial pressure and rate–pressure product (table IV)

The initial heart rates were 90 beat min^{-1} in group 2 and 73 beat min^{-1} in group 1. During anaesthesia and surgery heart rate varied between 77 and 96 beat min^{-1} in group 2 and between 69 and 83 beat min^{-1} in group 1. After intubation, heart rate decreased significantly in both groups, whereafter no significant differences were noted within or between the groups.

Initially, systolic arterial pressure was 141 mm Hg and 136 mm Hg in groups 1 and 2, respectively. Significant changes occurred after induction, with decreases to 95 and 104 mm Hg and increases (during surgery) to maximum values of 118 and 139 mm Hg, respectively. Systolic arterial pressures and rate–pressure product were significantly higher in group 2 during the two periods of active surgery (sampling points 5 and 7).

Blood-gas tensions

Arterial $P\text{CO}_2$ and $P\text{O}_2$ during anaesthesia were, respectively, 4.5 kPa and 20.0 kPa in group 1 and 4.7 kPa and 18.6 kPa in group 2.

DISCUSSION

Stress and anxiety are potent activators of the sympathoadrenal system. Adrenaline is released from the adrenal gland, and its plasma concentration can be regarded as an indicator of the degree of anxiety experienced. Noradrenaline in plasma comes mainly from the overflow of noradrenaline from sympathetic nerve terminals (Cryer, 1976). The initial adrenaline and noradrenaline concentrations in the two groups were similar to those reported in non-stressed, healthy individuals (Bühler et al., 1978), indicating that the patients were calm and free of anxiety.

During the induction of anaesthesia catecholamine concentrations and SAP either decreased or remained constant in both groups. There were no

TABLE IV. *Heart rate (beat min^{-1}), systolic arterial pressure (mm Hg) and rate–pressure product values (HR.SAP) (mean ± SEM). Significant differences: *from (1) group 1 (P < 0.05); †from (1) group 2 (P < 0.05); ‡from (2) group 1 (P < 0.05); °from (2) group 2 (P < 0.05); +from (3) group 1 (P < 0.05); §from (4) group 2 (P < 0.05); •from (5) group 2 (P < 0.05); ′from (6) group 2 (P < 0.05); ¶between HFA and BLA groups (P < 0.05)*

	HR		SAP		RPP	
Sample	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1
(1)	90±3	73±7¶	136±8	141±11	11771±1239	10132±2502
(2)	96±3†	83±10	110±5†	107±7*	10455±1235°	9069±4034
(3)	85±3°	76±9‡	104±10†	95±7*	8977±1860†	7436±3444
(4)	86±6	73±8	117±8†	100±7*	10037±1745	7478±2953
(5)	89±5	72±9	137±8°§	107±9*¶	11560±1792§	6947±1229*¶
(6)	81±8°	69±8‡	122±3	111±7*+	9248±1730•	7592±2248*
(7)	77±5†°	69±8‡	139±4°§′	118±8+¶	10569±2339′	*8028±2011¶

increases during intubation and the concentrations of adrenaline and noradrenaline remained low until the start of surgery. These findings accord with other studies which showed blunting of the circulatory response to intubation when thiopentone was combined with low doses of fentanyl (Dahlgren and Messeter, 1981; Martin et al., 1982).

Unlike other anaesthetic agents such as morphine, halothane and nitrous oxide, thiopentone, by itself, reduces sympathoadrenal activity (Joyce, Roizen and Eger, 1983), and to obtain the same degree of suppression with fentanyl alone would have required much larger doses than the 5 μg kg^{-1} given here. This has been shown in an earlier study (Hamberger and Järnberg, 1983), in which a dose of 10 μg kg^{-1} used in a neurolept anaesthesia induction sequence, without thiopentone, failed to suppress the increase in plasma adrenaline concentration associated with intubation. In that study, plasma adrenaline concentration varied significantly depending on the degree of surgical stress. Because of the short plasma half-life of adrenaline, interruption of surgery for 10 min was sufficient to allow the plasma adrenaline concentration to return to baseline values.

During surgery noradrenaline concentrations in both groups and the adrenaline concentration in group 2 increased, while the adrenaline concentrations in group 1 remained at their post-induction values during the entire surgical procedure. Plasma adrenaline concentration and the rate–pressure product were both significantly higher in group 2 during the two periods of active surgical stress. The catecholamine concentrations obtained during these periods were comparable to those found in previous studies, and during exercise (Galbo, Holst and Christensen, 1975) or hypoglycaemia (Garber et al., 1976). The intraoperative adrenaline concentrations in group 2 were comparable to those found by Stratton and colleagues (1985) to induce significant increases in HR and SAP, associated with an increase in cardiac output of approximately 60%. It is, therefore, probable that the differences in the catecholamine concentrations are reflected in the differences in rate–pressure product before and during surgery, and between the two groups.

Increased sympathoadrenal activity is caused by many factors, including surgical trauma/stress (Halter, Pflug and Porte, 1977), hypoxia, hypercarbia, haemorrhage and decreases in arterial pressure (Callingham, 1975). In this study, adequate oxygenation and ventilation were provided—as shown by the blood-gas tensions—and minimal blood loss occurred during the surgical procedure. Thus it may be reasonable to assume that the differences in sympathoadrenal activity observed were the result of an altered response to the stress of surgery, brought about by the different anaesthetic techniques.

The high-dose fentanyl anaesthesia technique is, at present, used almost exclusively in open-heart surgery, although fentanyl is usually given as an infusion of 200–300 μg min^{-1}. It has, however, been shown that the rapid administration of fentanyl, comparable to that used in this study (50 μg kg^{-1} min^{-1}) can be used without negative cardiovascular effects (Kentor, Schwalb and Lieberman, 1980). During coronary artery surgery, high-dose fentanyl anaesthesia has been shown to induce a stable haemodynamic state (Stanley, Philbin and Coggins, 1979; Zuric et al., 1982) without increases in plasma adrenaline concentration in the period before bypass (Stanley et al., 1980; Sebel et al., 1981). The low adrenaline concentrations in this study are comparable to those shown by Stanley and colleagues (1980) during a fentanyl–oxygen anaesthesia with fentanyl 75 μg kg^{-1}, but are slightly lower than in other studies.

High-dose fentanyl plus nitrous oxide in oxygen anaesthesia during upper abdominal surgery also reduces the perioperative metabolic response to surgery (Cooper et al., 1981; Haxholdt, Kehlet and Dyrberg, 1981), although the profound respiratory depression found in these patients immediately after the completion of surgery can be a major problem. In our study, this was prevented by maintaining the mechanical ventilation for a few hours into the postoperative period. Fentanyl was combined with oxygen and nitrous oxide in our patients because awareness during surgery has been reported during fentanyl–oxygen anaesthesia even with a bolus dose of fentanyl 150 μg kg^{-1}. No awareness was reported in either group.

The main indication for this type of anaesthesia, excluding cardiac surgery, would probably be major abdominal surgery. These operations usually take a long time and may be associated with large blood losses. Even after routine anaesthesia, such patients are usually transferred into the ICU, and extubation delayed. Especially in poor-risk cases such as patients with concomitant cardiovascular disease, the circulatory stability achieved during high-dose fentanyl anaesthesia could be advantageous.

The present study demonstrated significant differences between the high-dose fentanyl technique and the conventional balanced i.v. technique. Evidence of increased perioperative stress (measured by increases in plasma adrenaline concentration) was found in group 2, while group 1 remained essentially "stress free". Secondary to this, there was marked cardiovascular stability in group 1, while the rate–pressure product, which can be used as an index of myocardial oxygen consumption (Gobel et al., 1978), showed significant fluctuations in group 2. However, the overall effects of these differences on the whole organism during anaesthesia and operation require further clarification.

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LAPAROSCOPY: BLOOD-GAS VALUES AND MINOR SEQUELAE ASSOCIATED WITH THREE TECHNIQUES BASED ON ISOFLURANE

J. P. KENEFICK, A. LEADER, J. R. MALTBY AND P. J. TAYLOR

SUMMARY

Three anaesthetic techniques based on isoflurane were compared in outpatients undergoing laparoscopy. Sixty healthy patients were randomly allocated to receive isoflurane via mask (spontaneous respiration), via tracheal tube (spontaneous respiration) or via tracheal tube with controlled ventilation. Moderate hypercarbia occurred in the group breathing from a mask, although there was no further increase during carbon dioxide insufflation and laparoscopy. No arrhythmias were seen during insufflation and surgical conditions in all groups were good. Spontaneous respiration via a face mask did not lead to significant hypercarbia, acidosis or cardiac arrythmia. A high incidence of minor morbidity was found in all groups. Sore throat was much less frequent in the mask group, whereas the incidence of other after-effects, including muscle pains, did not differ significantly among the groups.

Gynaecological laparoscopy is a common outpatient procedure. The anaesthetic technique should be safe, and ensure rapid recovery with as few after-effects as possible. Two recent studies comparing different anaesthetic agents have reported a high incidence of post-operative complications such as sore throat, muscle pains, nausea and headache (Dhamee et al., 1982; Tracey, Holland and Unger, 1982). In these studies all patients received suxamethonium and tracheal intubation was performed.

A minority of anaesthetists, including one of the present authors (J.R.M.), allow patients undergoing laparoscopy to breathe spontaneously via an anaesthetic face mask (Scott and Julian, 1972; Kurer and Welch, 1984). However, one of the criticisms of this technique is that hypercarbia, especially in combination with halothane, may produce dangerous arrhythmias.

Isoflurane is not arrhythmogenic at Pa_{CO_2} values as high as 9.31 kPa (Cromwell et al., 1971) and may be a safer agent for laparoscopy. This study was designed to compare three different anaesthetic techniques (using isoflurane) with respect to respiratory status and cardiac arrhythmias during laparoscopy, and to evaluate postoperative morbidity.

PATIENTS AND METHODS

Approval for the study was obtained from the University of Calgary Joint Ethics Committee. Sixty women (all ASA class I or II) undergoing outpatient laparoscopy for investigation of infertility were studied. All gave informed consent for the insertion of a radial artery cannula to permit sampling for blood-gas analyses (Allen's test was performed on all patients). The patients were randomly allocated to one of three anaesthetic regimens.

Anaesthetic regimens (table I)

No premedication was given. The anaesthetics were all given by a consultant anaesthetist (J.P.K. or J.R.M.) and the laparoscopies performed by a consultant gynaecologist (A.L. or P.J.T.). All patients received thiopentone 6 mg kg^{-1} for induction of anaesthesia and this was followed by 65 % nitrous oxide and 2–3 % isoflurane in oxygen

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TABLE I. *Anaesthetic techniques and agents.* F_{IO_2} = *0.35 in all groups*

Group	Technique	Agents
I	Mask, spontaneous respiration	Thiopentone N_2O, O_2, isoflurane
II	Intubation, spontaneous respiration	Tubocurarine, thiopentone, suxamethonium N_2O, O_2, isoflurane
III	Intubation controlled ventilation $V_T = 10$ ml kg^{-1}; $f = 10$	Tubocurarine, thiopentone, suxamethonium N_2O, O_2, isoflurane 0.1% Suxamethonium infusion

administered via a circle system with carbon dioxide absorption. Patients in group I breathed spontaneously via a face mask; patients in groups II and III received tubocurarine 3 mg 3 min before suxamethonium 1.5 mg kg^{-1} and the trachea was intubated. Patients in group III received, in addition, an infusion of suxamethonium 1 mg ml^{-1}, and their lungs were ventilated with a tidal volume of 10 ml kg^{-1} at a rate of 10 b.p.m. Cuffed plastic 8.0-mm orotracheal tubes (National Catheter Corporation) without lubricant were used. Pharyngeal suction was performed on all patients in groups II and III before extubation, and on one patient in group I.

A 10° head-down tilt was used in all patients and the peritoneal cavity was distended with carbon dioxide using a Veress needle. The transmitted inflation pressure was recorded with the insufflating machine in the automatic mode. The duration of insufflation was similar in all groups (range 7–12 min).

Analgesics were not given routinely after the procedure and the requirements of the different groups were similar: 40–45% of patients received pentazocine 0.5–1 mg kg^{-1} in the recovery room, 22–30% received two 292 tablets (acetyl salicylic acid 375 mg, caffeine citrate 30 mg, codeine phosphate 30 mg) before leaving the hospital; 27–36% did not require any analgesic.

Assessment

The electrocardiogram was monitored from before the induction of anaesthesia until surgery was complete. After induction of anaesthesia a radial artery cannula was inserted and blood samples taken at the following times:

(1) with the patient in lithotomy position, but before insertion of the Veress needle;

(2) after maximum carbon dioxide insufflation;

(3) immediately before deflation, and

(4) 10 min after arrival in the recovery room.

Analysis of variance and Tukey's F test were used to analyse the arterial blood-gas results.

Morbidity after operation was assessed by means of a questionnaire. Patients completed this at the time of discharge from hospital—about 4 h after completion of surgery, and on the first and second days after operation. The results were analysed using the χ^2-test.

RESULTS

The three groups were similar in age, weight, volume of carbon dioxide insufflated and intra-abdominal pressure at maintenance of insufflation (table II).

After the induction of anaesthesia, five patients from group I and six patients from group II were slow to settle. Periods of breath holding were often observed before spontaneous respiration became regular. The administration of a further dose of thiopentone was necessary in some cases. Once stable anaesthesia had been established, conditions for laparoscopy were uniformly good in all groups.

No cardiac arrhythmia was observed in any group during the period of carbon dioxide pneumoperitoneum. However, in group III four patients showed transient ventricular bigeminy immediately following orotracheal intubation and before the insertion of the Verré needle. In each case the arrhythmia reverted spontaneously to sinus rhythm within 1 min.

Arterial blood-gas tensions are shown in table III. There was good oxygenation in all groups at all times. Moderate hypercarbia (6.38 kPa ± 1.06; 5.99 kPa ± 1.06) and moderate respiratory acidosis

TABLE II. *Comparison of age, weight, carbon dioxide volume and transmitted intra-abdominal pressure reading in each group (mean ± SD). * Baseline pressure, with Veress needle open to air, 8–10 mm Hg*

Group	Technique	Age (yr)	Weight (kg)	Volume of CO_2 insufflated (litre)	Transmitted insufflation pressure (mm Hg)*
I	Mask, spont. resp.	28.2±3.8	60.5±8.1	3.05±0.72	14.7±2.6
II	Intubated, spont. resp.	29.0±4.1	59.0±9.2	3.10±0.74	15.0±3.5
III	Intubated, IPPV	29.8±3.5	59.4±6.6	3.02±0.52	14.8±3.1

TABLE III. *Blood-gas values (±SD). (1) = With patients in lithotomy position before insertion of Veress needle; (2) = after maximal insufflation of carbon dioxide; (3) = at completion of laparoscopy before deflation; (4) = 10 mn after arrival in recovery room*

	(1) Baseline			(2) Max insufflation			(3) Before deflation			(4) Recovery Room		
Group:	I	II	III	I	II	III	I	II	III	I	II	III
pH	7.30 ±0.05	7.38 ±0.05	7.43 ±0.05	7.28 ±0.06	7.31 ±0.04	7.43 ±0.05	7.28 ±0.06	7.29 ±0.06	7.40 ±0.05	7.37 ±0.03	7.37 ±0.02	7.38 ±0.02
CO_2(kPa)	6.12 ±0.67	4.65 ±0.67	4.12 ±0.53	6.38 ±1.06	5.72 ±0.80	4.12 ±0.67	6.38 ±1.06	5.99 ±1.06	4.26 ±0.80	4.65 ±0.53	4.65 ±0.53	4.52 ±0.40
O_2 (kPa)	17.42 ±4.92	21.41 ±4.39	22.61 ±4.66	17.42 ±4.12	17.02 ±3.99	18.35 ±3.46	17.69 ±4.12	17.56 ±4.66	18.62 ±3.72	18.09 ±5.19	17.42 ±5.99	18.49 ±5.19

(pH 7.28±0.06; 7.29±0.06) were noted in groups I and II immediately before deflation of the pneumoperitoneum. However, these figures did not differ significantly from the baseline values for group I patients in the lithotomy position before the creation of the pneumoperitoneum. The baseline values for group II, which were similar to those for group III, reflect the effects of the manual ventilation required before spontaneous breathing was resumed. Patients in group III demonstrated moderate hypocarbia (4.26 kPa ± 1.06) and no acidosis (pH 7.40±0.05) immediately before the deflation of pneumoperitoneum.

One patient in group I, who was moderately obese and smoked 40 cigarettes per day, had a stormy induction. She salivated, coughed repeatedly, and developed laryngospasm. She took several minutes to settle into smooth anaesthesia. The baseline arterial blood-gas sample, taken during this episode, showed a pH of 7.16. Smooth anaesthesia was eventually achieved and the laparoscopy completed. pH values during the pneumoperitoneum showed steady improvement. The problems in this patient were attributed to the irritant isoflurane vapour in an unpremedicated heavy smoker. One patient (group I) and one in group II had pH values of 7.19 and 7.16, respectively, immediately before deflation of the pneumoperitoneum, but their clinical condition gave no cause for concern. The acid–base status of all patients in the recovery room was satisfactory.

The symptoms reported after the procedure are shown in table IV. At the time of discharge from hospital the most common symptoms were general weakness (68%), drowsiness (45%), shoulder pain (50%) and muscle ache (48%). Sore throat was present in 10% of the mask group and 28% of the intubated groups; however, this difference was not significant ($P > 0.05$).

Twenty-four hours later, the most frequent complaint was pain in the shoulder area (65%) and general muscle ache (55%). There were no significant differences between the groups. Sore throat was present in 65% of intubated patients, and in 10% of the non-intubated patients; this difference was significant ($P < 0.0005$).

By the 2nd day after operation all symptoms were less frequent, although some minor discomfort still persisted, especially aching in the shoulder and muscles.

TABLE IV. *Postoperative morbidity in three groups of 20 patients. Number (% of group) with each symptom.* * $P < 0.0005$ *group I v. group II v. group III on 1st day*

	Discharge from hospital			1st day after op.			2nd day after op.		
Group:	I	II	III	I	II	III	I	II	III
Drowsiness	10 (50)	9 (45)	8 (40)	5 (25)	4 (20)	6 (30)	2 (10)	3 (15)	1 (5)
Dizziness	5 (25)	9 (45)	7 (35)	2 (10)	4 (20)	5 (25)	0 (0)	3 (15)	3 (15)
Headache	9 (45)	4 (20)	4 (20)	4 (20)	4 (20)	2 (10)	2 (10)	2 (10)	1 (5)
Sore throat	2 (10)	6 (30)	5 (25)	2 (10)*	14 (70)*	12 (60)*	1 (5)	4 (20)	2 (10)
Weakness	15 (75)	15 (75)	11 (55)	9 (45)	10 (50)	7 (35)	2 (10)	7 (35)	3 (15)
Nausea	4 (20)	5 (25)	3 (15)	3 (15)	3 (15)	3 (15)	3 (15)	2 (10)	1 (5)
Vomiting	1 (5)	1 (5)	1 (5)	0 (0)	1 (5)	2 (10)	0 (0)	1 (5)	0 (0)
Pain in shoulder	9 (45)	14 (70)	9 (45)	13 (65)	16 (80)	10 (50)	9 (45)	8 (40)	4 (20)
Muscle ache	7 (35)	13 (65)	9 (45)	8 (40)	14 (70)	11 (55)	6 (30)	7 (35)	7 (35)

DISCUSSION

Early reports of anaesthesia for laparoscopy using halothane emphasized the dangers of hypercarbia if patients were allowed to breathe spontaneously (Desmond and Gordon, 1970; Calverley and Jenkins, 1973). These authors condemned the practice of spontaneous respiration via a face mask, but others disagreed (Lewis et al., 1972; Scott and Julian, 1972). More recently, Kurer and Welch (1984) found no significant differences in intraoperative anaesthetic or surgical complications between patients breathing halothane via a face mask and those in whom ventilation was controlled via a tracheal tube. Both techniques are equally popular in their hospital. The duration of insufflation was usually less than 5 min. The authors concluded that the safety of the procedure probably depends less on the particular technique than on a short operative time, close intraoperative monitoring, and the experience of both anaesthetist and surgeon.

Stability of cardiac rhythm is a feature of isoflurane anaesthesia. A study of three anaesthetic techniques using this newer agent was felt to be justified. The first objective was to determine whether spontaneous respiration using isoflurane during laparoscopy caused hypercarbia, acidosis or cardiac arrhythmia. A second objective was to assess postoperative morbidity and to determine whether postoperative symptoms were influenced by the different anaesthetic techniques.

Oxygenation in all patients was good throughout the period of study. Hypercarbia (6.38 kPa ± 1.06) was present, as expected, in group I during carbon dioxide pneumoperitoneum. However, this was only minimally greater than the baseline value in the same patients in the lithotomy position before the insertion of the Veress needle (6.12 kPa ± 0.67.). In healthy young patients, and in the absence of other problems, this is unlikely to be dangerous. The baseline figures in group II reflect manual ventilation before patients resumed spontaneous respiration. There was no significant increase in Pa_{CO_2} in any group during the laparoscopy itself while the pneumoperitoneum was maintained. Ten minutes after arrival in the recovery room, all three groups had virtually identical blood-gas tensions.

In the two groups of patients who breathed spontaneously, moderate acidosis developed during the carbon dioxide pneumoperitoneum. During insufflation there was no concern about the clinical condition of any of these patients. However, they were almost all healthy, young, non-obese women and the duration of the procedure was brief. Spontaneous respiration, whether via mask or tracheal tube cannot be recommended for obese or less healthy patients, nor when the laparoscopy may be prolonged, as for oocyte retrieval for *in vitro* fertilization.

The risk of arrhythmias during spontaneous respiration and carbon dioxide pneumoperitoneum was not confirmed in this study. No arrhythmia was recorded in any group during peritoneal insufflation. Immediately following orotracheal intubation, four patients in group III showed transient ventricular bigeminy which disappeared spontaneously within 1 min. It is known that such arrhythmias may be related to the stimulus of intubation and usually do not require specific treatment (Atkinson, Rushman and Lee, 1982).

It has been shown that both inpatients and outpatients undergoing general anaesthesia are at theoretical risk of regurgitation and aspiration of acid stomach contents (Ong, Palahniuk and Cumming, 1978; Miller, Wishart and Nimmo, 1983). Passive regurgitation of gastric contents into the pharynx may occur in any patient, but inhalation of foreign material deep into the bronchial tree can only occur if laryngeal and cough reflexes are abolished by the use of neuromuscular blocking drugs or deep inhalation anaesthesia. Patients breathing spontaneously under light general anaesthesia, without a tracheal tube, usually maintain the cough reflex and the integrity of the crico-pharyngeal sphincter (Davies, 1979). Scott (1980) has pointed out that, in a series of 50000 patients undergoing laparoscopy studied prospectively in the United Kingdom, of whom approximately 5000 were not intubated, there was no case of inhalation of gastric contents. An even larger series would be needed to show that intubation provides safer conditions, and no such study has yet been reported.

The pungent nature of isoflurane vapour makes it a more difficult agent than halothane to use with spontaneous respiration (Corall, 1983). In the present study some patients were slow to settle although, once smooth anaesthesia was established, surgical conditions were excellent.

The study confirmed that there is a high incidence of morbidity after laparoscopy no matter which agent or technique is used. Dhamee and colleagues (1982) compared fentanyl, halothane and enflurane and found that drowsiness, dizziness, headache and weakness were more frequent than in the present study. In the fentanyl group vomiting occurred in 43% of patients and persisted into the first day after operation in 28% of patients. Tracey, Holland and Unger (1982) compared halothane, enflurane and isoflurane. Their observations for halothane and enflurane were similar but, of patients who received isoflurane, 40% could still smell the anaesthetic and (44%) complained of headache the next day. In view of the low solubility of isoflurane, these results are rather surprising.

In the present study it was expected that there would be a much lower incidence of sore throat and muscle pains when orotracheal intubation using suxamethonium was avoided. This was true for sore throats in the non-intubated patients (10% *v.* 65%) on the first day. However, there was no significant difference in the incidence of muscle pains between the groups and this suggests that muscle pains are related more to the surgical procedure than to the anaesthetic agents or technique. The incidence of other symptoms did not show statistically significant differences between the groups.

This study has confirmed the high incidence of minor morbidity following laparoscopy. Spontaneous respiration with a mask using isoflurane produced good operative conditions without dangerous hypercarbia, acidosis or cardiac arrhythmias, and the decreased frequency of postoperative sort throat appeared to be a major advantage.

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EFFECTS OF ATRACURIUM AND VECURONIUM ON THE LATENCY AND THE DURATION OF THE NEGATIVE DEFLECTION OF THE EVOKED COMPOUND ACTION POTENTIAL OF THE ADDUCTOR POLLICIS

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SUMMARY

The effect of atracurium or vecuronium on the depolarization phase of the evoked compound action potential of the adductor pollicis has been investigated in 30 adult patients. Patients were studied using single supramaximal stimulation of the ulnar nerve at the wrist. The evoked compound action potential was measured over the adductor pollicis muscle. When blockade by atracurium exceeded 80%, a significant decrease in latency was recorded ($P < 0.05$)*. There was no significant change in latency after vecuronium. During the onset of blockade, depression of the amplitude of the evoked compound action potential was associated with a prolongation of its duration* ($P < 0.05$)*. The mean maximum increase in the negative deflection time was found to be similar after atracurium and after vecuronium. However, this phase was prolonged to a greater extent for a given degree of amplitude depression during the onset of blockade by atracurium* ($P < 0.05$)*.*

Increasingly, electromyography is being used to monitor neuromuscular transmission during anaesthesia. Depression of the amplitude of the evoked compound action potential (ECAP) of the adductor pollicis is a widely accepted index of neuromuscular blockade. However, the waveform of the ECAP may change in respects other than amplitude as blockade progresses. The latency of single muscle-fibre action potentials may vary slightly, and it has been observed that the normal variation in latency increases during partial neuromuscular blockade by tubocurarine (Ekstedt and Stalberg, 1969). It would, therefore, be informative to investigate the time course of the ECAP during the onset of blockade following the injection of either atracurium or vecuronium. Atracurium and vecuronium were chosen as they may have dissimilar actions at the neuromuscular junction (Black et al., 1985).

PATIENTS AND METHODS

Thirty adult patients (ASA I) undergoing elective surgery were investigated after they had given informed consent to the study which had been approved by the Hospital Ethical Committee. Patients were allocated randomly to three groups: a control group of patients who received no neuromuscular blocking drug, and patients who received either atracurium or vecuronium.

Neuromuscular transmission was investigated as follows: the ulnar nerve was stimulated at the right wrist with single supramaximal square wave pulses of 0.2 ms duration at 20-s intervals. ECG-type electrodes were used for stimulation and recording (Medicotest Q.00.S). Since the position and geometry of the electrodes influence the shape of the ECAP (Lynn et al., 1978), a standardized electrode position was used to minimize this source of variability. The active electrode was placed over the motor point of the

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adductor pollicis and the inactive electrode over the head of the second metacarpal. The ECAP of the adductor pollicis was band-pass filtered between 2 Hz and 10 kHz, amplified, and displayed using a storage oscilloscope incorporating a time measurement cursor with a discrimination of 0.08 ms (Medelec MS91 electromyography system). The gain of the system was adjusted to produce an ECAP amplitude of between 10 and 20 mV during the control period in each patient. A permanent record was obtained on heat sensitive paper via a digital buffer. The amplitude of the ECAP was measured from the peak negative deflection to the isoelectric line. Percentage blockade was derived for each patient from the depression of the amplitude compared with three, pre-blockade control values.

For the purpose of this investigation, the time from the stimulus artefact to the instant at which the ECAP crossed the isoelectric line was defined as the negative deflection time (NDT) (fig. 1). Latency was defined as the time from the stimulus artefact to the time at which the signal first deviated towards negativity (fig. 2). Premedication with papaveretum 10–20 mg and hyoscine 0.2–0.4 mg was given i.m. 1 h before operation. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1}, and maintained with fentanyl 1.5 $\mu g\ kg^{-1}$ i.v., given concurrently with the next stimulus and flushed through the cannula with physiological saline. Additional thiopentone was given if required. The doses of the neuromuscular blockers were those reported in a previous study (Black et al., 1985) to produce an expected 95% depression of ECAP amplitude (ED_{95}). The ECAP was recorded until blockade was maximal, or for 6 min in the control group.

TABLE I. *Changes in ECAP depression and NDT with time in the control group* (n = *10*)

Time (min)	Mean % ECAP depression (±SEM)	Mean % change NDT (±SEM)
1	1.5 (0.92)	−1.25 (0.33)
2	2.3 (0.97)	−1.41 (0.59)
3	3.2 (1.34)	−2.01 (0.67)
4	3.1 (1.46)	−2.53 (0.67)
5	3.0 (1.48)	−2.85 (0.65)
6	3.1 (1.46)	−2.95 (0.74)

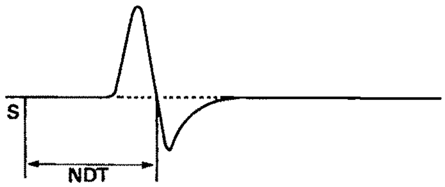

FIG. 1. Schematic diagram of an ECAP showing the NDT which is the time from the stimulus artefact (S) to the point at which the ECAP crosses the iso-electric line.

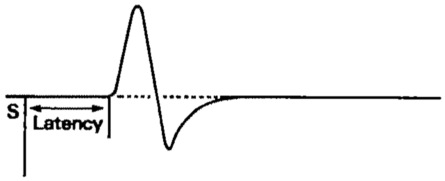

FIG. 2. Schematic diagram of an ECAP indicating the duration of latency.

RESULTS

There were no significant differences (analysis of variance) between the three groups of patients with respect to their mean ages or weights. In the control group an apparent decrease in the NDT occurred during the period of measurement (table I), but the change was not significant (one-way analysis of variance). A scattergram of all the measurements of percentage change of ECAP amplitude and NDT after the injection of atracurium is shown in figure 3. A small decrease in NDT was followed by a general increase as blockade progressed. This increase in NDT became more marked in the presence of profound blockade. The changes in NDT associated with blockade by vecuronium are shown in figure 4. In order to examine any difference between the effects of atracurium and vecuronium, all the measurements included in each group were divided into ranks, each spanning an arbitrary 10% of ECAP amplitude depression (table II). The maximum mean total change in NDT was about 13% in both groups. The NDT was prolonged at an earlier stage of blockade by atracurium than by vecuronium and the difference between the groups was significant (Student's *t* test) ($P < 0.05$) between 50 and 90% amplitude depression.

The percentage changes in latency in each rank of ECAP amplitude depression were also compared (table III). There was a significant decrease in latency when the 0–10% blockade interval was compared with the 80–100% blockade intervals in

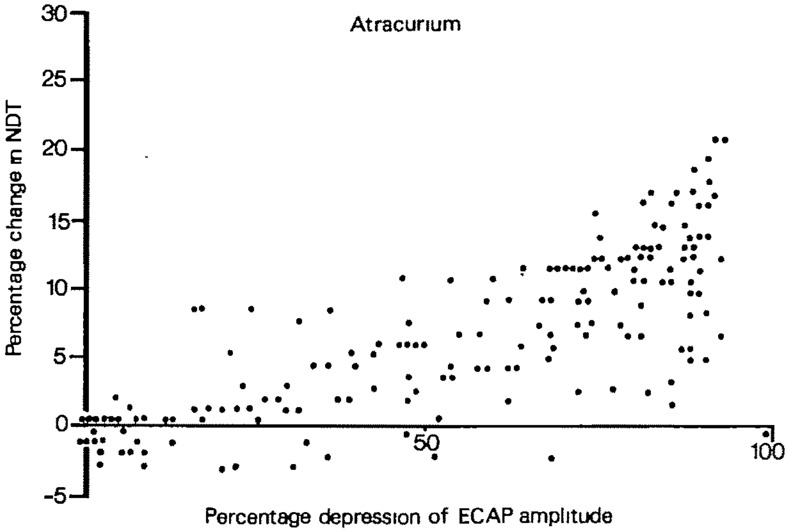

FIG. 3. Scattergram of percentage change of NDT and percentage depression of ECAP amplitudes in the atracurium group ($n = 10$).

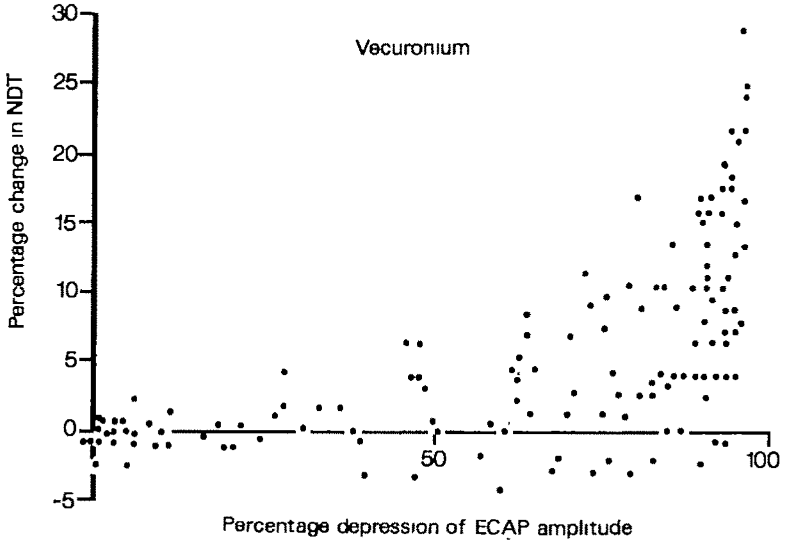

FIG. 4. Scattergram of percentage change of NDT and percentage depression of ECAP amplitudes in the vecuronium group ($n = 10$).

those patients who received atracurium ($P < 0.05$). In the patients who received vecuronium, no significant differences were found. When the atracurium and vecuronium groups were compared, significant differences were found between the groups at the 80–90% and 90–100% blockade intervals ($P < 0.05$) (Student's t test).

DISCUSSION

We have demonstrated that, during the onset of blockade associated with atracurium or vecuronium, depression of the amplitude of the ECAP was associated with prolongation of its duration. The mechanism underlying this effect has not

TABLE II. *Mean percentage changes in NDT during onset of blockade by atracurium and vecuronium. The changes associated with atracurium and vecuronium were significantly different:* *$P < 0.05$; **$P < 0.01$ (*Student's* t *test*)

Percentage depression of ECAP amplitude	Mean % change in NDT (±SEM) Atracurium		Vecuronium
0–10	−0.53 (0.37)		−0.74 (0.18)
10–20	2.0 (1.13)		−0.52 (0.33)
20–30	1.68 (1.06)		1.19 (0.84)
30–40	2.44 (0.90)		0.67 (0.45)
40–50	4.96 (0.72)		2.94 (1.51)
50–60	5.19 (1.03)	**	0.12 (0.78)
60–70	7.10 (0.93)	*	3.31 (1.25)
70–80	9.88 (0.63)	*	5.79 (1.44)
80–90	11.52 (0.70)	*	8.26 (1.02)
90–100	13.0 (0.93)		13.53 (1.04)

TABLE III. *Mean percentage changes in latency during onset of blockade by atracurium and vecuronium. A significant reduction in latency occurred between 0–10% and 80–100% depression of ECAP amplitude in those patients who received atracurium:* †$P < 0.05$; ††$P < 0.01$ (*Student's* t *test*). *The changes associated with atracurium and vecuronium were significantly different between an 80–100% depression of ECAP amplitude:* *$P < 0.05$; **$P < 0.01$ (*Student's* t *test*)

Percentage depression of ECAP amplitude	Mean % change in latency (±SEM) Atracurium		Vecuronium
0–10	3.05 (0.57)		3.11 (0.43)
10–20	3.19 (0.66)		3.08 (0.45)
20–30	3.22 (0.73)		3.22 (0.28)
30–40	3.42 (0.66)		3.13 (0.40)
40–50	2.96 (0.42)		3.08 (0.46)
50–60	3.04 (0.41)		3.35 (0.42)
60–70	2.89 (0.36)		3.14 (0.45)
70–80	2.98 (0.44)		3.07 (0.38)
80–90	†2.81 (0.30)	*	3.03 (0.40)
90–100	††2.64 (0.18)	**	3.01 (0.51)

been identified, but this change was not seen in the control group, which suggests that the changes observed after atracurium or vecuronium were unlikely to reflect a time-related effect. It is possible to suggest several sites at which a drug may increase the time from nerve stimulation to the end of the gross depolarization phase of the muscle. Conduction velocity in motor nerves is increased by gallamine (Thornton, Whelpton and Brown, 1968) and a similar effect of atracurium might explain the decrease in latency observed with this drug. The main effect on NDT is, therefore, likely to be intrajunctional or in the propagation of the muscle fibre action potentials throughout the adductor pollicis. It has been established that the velocity of propagation of the muscle action potential in single muscle fibres is unaffected by tubocurarine (Stalberg, 1966). A differential increase in the latency of some or all of the muscle action potentials may produce a temporal expansion of the ECAP. However, we have demonstrated that the latency of the compound muscle action potential decreases after atracurium and remains unchanged after vecuronium. Therefore, the increase in NDT is predominantly the result of an increase in the duration of the negative phase of the gross compound action potential and not of an increased delay in its onset. As neuromuscular blockade progresses, increasing numbers of individual muscle fibres fail to reach the threshold required for an action potential. In addition, the time required for the end-plate potentials to increase to this threshold may be increased to a greater extent in some fibres in response to blockade of pre- and post-junctional cholinoceptors. These events may tend to disrupt the temporal and spatial activation of the remaining fibres and, hence, prolong the gross compound action potential recorded by surface electrodes—in addition to reducing its amplitude.

Although the mean maximum increase in NDT was similar after atracurium and vecuronium, the NDT was prolonged to a greater extent for a given degree of amplitude depression during the onset of blockade by atracurium. This suggests that separate mechanisms may be responsible for the attenuation of ECAP amplitude and the prolongation of the depolarization phase. One possible explanation is a greater susceptibility of a particular type or types of fibre to vecuronium than to atracurium. In a muscle comprising discrete groups of fibres of mixed susceptibility, the electrical contribution of the remaining unblocked fibres to the gross compound action potential would be expected to be more uniform in nature. The component action potentials constituting the ECAP might then produce a more synchronous compound action potential and with a smaller increase in NDT than if fibres were inactivated at random. If, in contrast, the shape of the ECAP reflects not the degree of synchronization, but the duration, and hence frequency, of the individual muscle fibre action potentials, preferential blockade of the fast fibres would result in greater slowing of the ECAP wave form. This theory would predict that fast muscle fibres would be blocked more rapidly by atracurium than slow fibres.

Present knowledge suggests that atracurium and vecuronium act predominantly at post-junctional receptors (Calvey et al., 1983; Baird, Bowman and Kerr, 1982). However, a pre-junctional action of atracurium has been demonstrated in the motor nerve endings of the cat soleus (Baker, Stanec and Loundes, 1984), and the existence of synergism when atracurium and vecuronium are given together (Black et al., 1985) supports the hypothesis that these two drugs may differ in their mechanisms of action. The suggestion that differences in the response of a muscle of mixed fibre type to atracurium could be attributed, in part, to differences in the predominance of the pre- and post-junctional receptors in each fibre type is at present speculative. Further investigation is necessary in order to elucidate the differences between the mechanisms of action of atracurium and vecuronium at receptor level.

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CHANGES IN THE POWER SPECTRUM OF THE EVOKED COMPOUND ACTION POTENTIAL OF THE ADDUCTOR POLLICIS WITH THE ONSET OF NEUROMUSCULAR BLOCKADE

N. J. N. HARPER, N. D. PUGH, T. E. J. HEALY AND H. V. PETTS

Measurement of the evoked compound action potential (ECAP) has considerable theoretical and practical advantages over the measurement of the force of muscular contraction (Calvey, 1984) as a monitor of neuromuscular transmission. The ECAP may also yield information about the action of neuromuscular blocking drugs at receptor level. It has been observed that, during the onset of neuromuscular blockade by atracurium or vecuronium, the decrease in amplitude of the ECAP is associated with an increase in the duration of the negative deflection of the waveform (Pugh et al., 1985). The mechanism responsible for this change is, as yet, unexplained.

Fourier analysis may be used to reveal the relative power of the harmonics of the fundamental frequency which, in combination, comprise the recorded signal. A shift in the component harmonics of the signal towards lower frequencies may be expected to increase the duration of the ECAP.

It would be instructive to investigate the power spectrum of the ECAP by Fourier analysis during blockade by atracurium or vecuronium, and to establish the relation between the increase in duration of the compound action potential and any change in frequency components.

SUMMARY

The effects of neuromuscular blockade by atracurium and vecuronium on the power spectrum of the evoked compound action potential (ECAP) of the adductor pollicis were investigated in 30 adult patients undergoing elective surgery. The changes in amplitude and mean power frequency (MPF) of the ECAP were measured. Ten patients received an ED_{95} (0.23 mg kg^{-1}) of atracurium and 10 received an ED_{95} (0.055 mg kg^{-1}) of vecuronium. The remaining 10 patients did not receive any neuromuscular blocking drug, and were monitored for 6 min to exclude any time-related changes in the ECAP. Neuromuscular blockade produced a decrease in total power and a shift towards lower frequencies. This was reflected in a decrease in the MPF in those patients receiving atracurium or vecuronium. There was no significant difference ($P < 0.05$) between the atracurium and vecuronium groups in the magnitude of the change in MPF. These findings suggest that the previously reported increase in the duration of the negative deflection of the ECAP is predominantly the result of a change in its frequency components.

PATIENTS AND METHODS

Thirty adult patients (ASA I or II) aged 18–65 yr undergoing elective surgical procedures were investigated after they had given informed consent to the study, which had been approved by the Hospital Ethical Committee. All the patients had normal renal and hepatic function and were not taking any medication known to affect neuromuscular transmission. Patients were randomly allocated to three equal groups.

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Premedication with papaveretum 10–15 mg and hyoscine 0.2–0.3 mg was given i.m. approximately 90 min before the induction of anaesthesia. Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and maintained with fentanyl 1.5 μg kg^{-1} and 70% nitrous oxide in oxygen. Ventilation was assisted, when necessary, to maintain normocapnia. The majority of patients received additional supplements of thiopentone up to 2 mg kg^{-1} to maintain anaesthesia during the period of measurement.

Following the induction of anaesthesia, neuromuscular transmission was investigated as follows. The ulnar nerve at the right wrist was stimulated with single supramaximal square wave pulses of 0.2 ms duration at 20-s intervals. ECG-type electrodes were used for stimulating and recording (Medicotest Q.00.S). The ECAP of the adductor pollicis was recorded using standard electrode geometry (Pugh et al., 1985). The skin was carefully prepared with acetone using mild abrasion. The active electrode was positioned over the motor point of the adductor pollicis and the inactive electrode over the head of the second metacarpal. An indifferent electrode was placed on the dorsal aspect of the hand. The signal was detected and recorded using a diagnostic electromyograph (Medelec MS.91) and an Apple IIe computer. The amplitude of the ECAP was measured from the negative peak to the iso-electric line and the extent of blockade was expressed as the percentage depression of the amplitude compared with the mean of three control (pre-blockade) readings. This apparatus enabled the signal to be band-pass filtered between 2 Hz and 10 kHz, amplified and displayed on an oscilloscope. The output of the amplifier was passed through an analogue-to-digital converter (ADC) and stored in a digital buffer for subsequent computer analysis. A permanent record (on heat sensitive paper) was also obtained via the ADC (Medelec MS.91). The system was able to reproduce faithfully a sine wave of higher frequency than those encountered within the ECAP signal.

After an initial period to allow electrode settling, the ECAP amplitude became stable and was observed for 1 min, after which three consecutive compound action potentials were recorded (pre-blockade controls). Patients in groups 1 and 2 then received atracurium 0.23 mg kg^{-1} or vecuronium 0.055 mg kg^{-1} i.v. These doses were expected to produce 95% depression of the amplitude of the ECAP (Black et al., 1985). The third group of patients did not receive any neuromuscular blocking drug. The ECAP was recorded until the amplitude was depressed maximally, or for 6 min in the control group.

An Apple IIe microcomputer was used to calculate the power spectrum of each ECAP by Fourier analysis. In order to obtain discrimination of approximately 2 Hz, a trace duration of 500 ms was chosen. The number of data points was constrained to an exact power of 2 and 1024 (2^{10}) data points were used in the transformation. Since the MS.91 produces 1000 bytes of information for each trace, the last 24 data points were assigned a value of zero. The signal was digitized at a rate of 2 kHz and the stimulus artefact and baseline drift removed digitally. The frequency spectrum of the ECAP was calculated using a fast Fourier transform technique (Bergland, 1972). This produced estimates of the power at 1.95-Hz intervals within a 0–500 Hz band width. The upper limit of 500 Hz was sufficient to contain the entire frequency content of the ECAP measured from the adductor pollicis (Mills, 1982). The mean power frequency (MPF) of the spectrum (that is, the frequency at which one-half the total power is at frequencies greater than the MPF, and one-half at frequencies less than the MPF) was then calculated (Mills, 1982).

RESULTS

There were no significant differences (analysis of variance) between the three groups of patients with respect to mean age or weight. A typical ECAP is shown in figure 1. In the control group there appeared to be a small decrease in ECAP amplitude and MPF (table I). However, during the period of measurement (6 min) this was not significant (analysis of variance). Neuromuscular blockade produced a decrease in total power

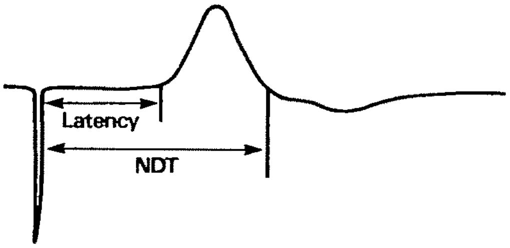

FIG. 1. A typical ECAP of the adductor pollicis illustrating the latency and negative deflection time (NDT).

TABLE I. *Changes in ECAP amplitude and MPF with time in the control group*

Time (min)	Mean % depression of ECAP amplitude (±SEM)	Mean % depression of MPF (±SEM)
1	−0.1 (0.69)	−0.4 (0.40)
2	1.1 (0.55)	1.3 (0.47)
3	1.6 (0.70)	2.3 (0.63)
4	2.4 (0.68)	2.3 (1.63)
5	1.0 (0.74)	2.8 (1.30)
6	1.4 (0.74)	3.0 (1.19)

accompanied by a shift towards lower frequencies (fig. 2). The scattergram of all the measurements of percentage change of ECAP amplitude and MPF following the administration of atracurium is shown in figure 3. An initial small increase in MPF was followed by a marked decrease in the presence of profound blockade. Similar changes in MPF were observed in association with blockade by vecuronium (fig. 4). In order to examine any differences between the effects of atracurium and vecuronium, all the measurements included in each group were divided into ranks, each spanning an arbitrary 10% of ECAP

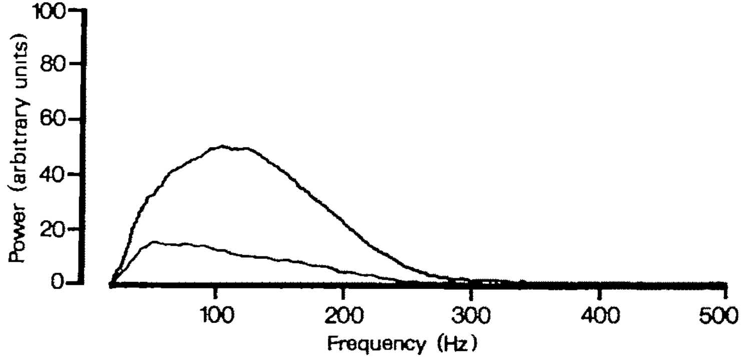

FIG. 2. Decrease in total power and shift towards lower frequencies produced by neuromuscular blockade.

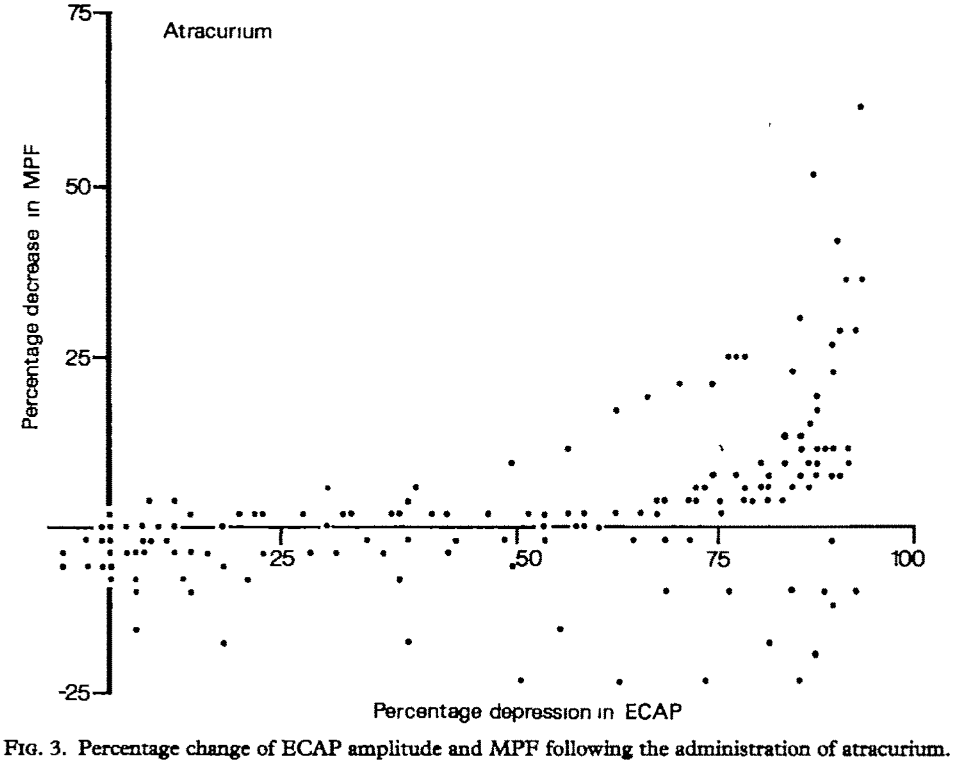

FIG. 3. Percentage change of ECAP amplitude and MPF following the administration of atracurium.

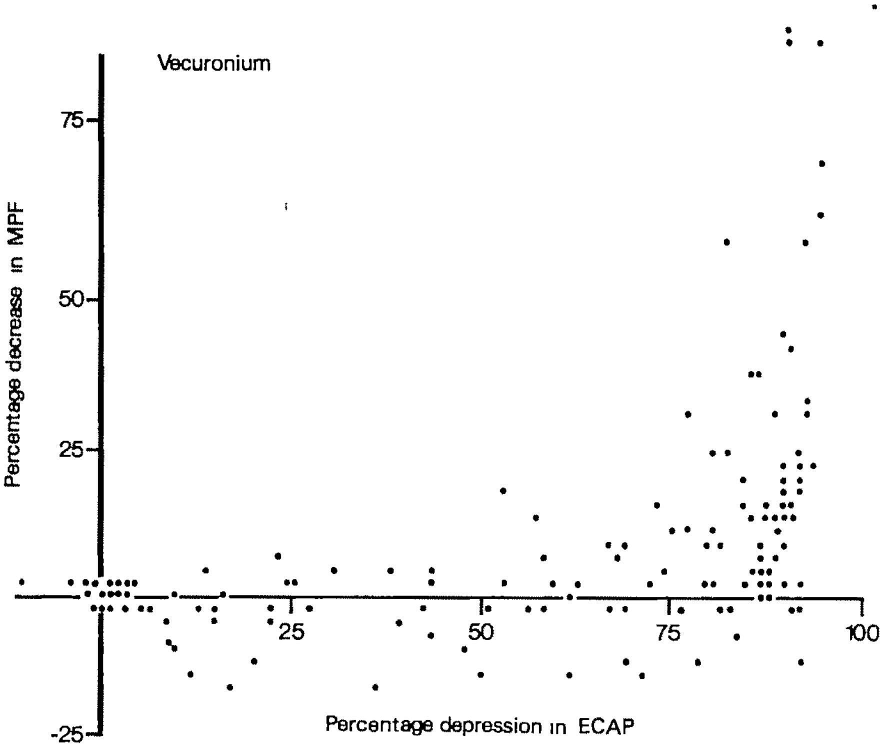

FIG. 4. Percentage change of ECAP amplitude and MPF following the administration of vecuronium.

TABLE II. *Changes in ECAP amplitude and MPF after the administration of vecuronium and atracurium.* $^{*}P < 0.05$; $^{**}P < 0.01$

Percentage depression in ECAP amplitude	Mean % depression in Mean Power Frequency (± SEM)	
	Vecuronium	Atracurium
0–10	−1.78 (0.29)	−2.68 (0.44)
10–20	−6.56 (2.01)*	−4.60 (1.37)
20–30	−4.85 (2.01)	−3.83 (3.52)
30–40	−3.50 (4.63)	−1.55 (1.94)
40–50	−4.28 (1.58)	−0.20 (1.36)
50–60	0.12 (3.26)	−1.91 (2.72)
60–70	−2.37 (2.66)	1.75 (2.95)
70–80	2.58 (3.30)	3.17 (2.69)**
80–90	9.03 (2.43)**	8.71 (1.79)**
90–100	25.36 (4.42)**	16.72 (4.00)**

amplitude depression (table II). The differences in mean MPF change were analysed using Student's unpaired *t* test. Patients who received atracurium exhibited significant differences between the percentage MPF change in the 0–10% blockade intervals compared with those in the 70–80%, 80–90% and 90–100% intervals ($P < 0.01$). In those patients who received vecuronium, significant differences were observed when the MPF of the 0–10% blockade interval was compared with those of the 10–20% ($P < 0.05$), 80–90% and 90–100% ($P < 0.01$) intervals.

When the atracurium and vecuronium groups were compared, there were no significant differences between the mean changes in MPF at each level of amplitude depression (Student's *t* test, $P > 0.05$).

DISCUSSION

In the present study we have demonstrated that neuromuscular blockade by atracurium and vecuronium is associated with a shift in the frequency spectrum of the ECAP of the adductor pollicis towards lower frequencies. In a previous investigation of the changes in the waveform of the ECAP during the onset of blockade, Pugh and colleagues (1985) demonstrated an increase in the duration of the negative deflection (negative deflection time: NDT). This was defined as the time from the stimulus artefact to the point at which the signal crossed the iso-electric line. The latency component of this measurement (fig. 1) was significantly reduced by atracurium and was unchanged by vecuronium. It is, therefore, unlikely that the increase in NDT was simply the result of a uniform increase in the delay between nerve stimulation and the generation of each motor unit potential. This suggests that, as neuromuscular blockade proceeds, there is a change in the pattern in which motor units are activated. A possible explanation would be a non-uniform increase in the latency of motor units. This could be described as desynchronization. A second possible mechanism is a relative increase in the duration of those motor unit action potentials which remain unblocked by the neuromuscular blocker. This may be consequent upon preferential blockade of those motor units with action potentials of short duration.

Power spectrum analysis apportions the total power contained within a signal to defined frequency bands; in this study 2-Hz bands within a total band width of 500 Hz. Because of the reciprocal relation between frequency and wavelength, component waveforms with a short wavelength will be represented at the upper end of the frequency spectrum. Power spectrum analysis removes the effect of phase from the constituent harmonic frequencies. Changes in latency of individual muscle fibre action potentials are, therefore, unlikely to affect the power spectrum.

Krakau (1956) has demonstrated that the Fourier spectrum of a single pulse is the same as that of a number of identical pulses firing in a manner which may be coherent, random or overlapping. If the assumption is made that motor unit action potentials are similar, their frequency components and those of muscle fibre action potentials may be reflected in the power spectrum of the ECAP. A shift towards lower frequencies demonstrated in the power spectrum of the EMG activity of voluntarily contracting muscle during fatigue studies in man has been ascribed to preferential fatigue of different species of motor unit. This phenomenon has been observed using either needle electrodes or electrodes placed on the surface of the skin (Kogi and Hakamada, 1962; Kaiser and Petersen, 1963; Kadefors, Kaiser and Petersen, 1968). Type 2b (fast twitch, fast fatigue) motor units fatigue less readily than slow, type 1 and type 2a (fast twitch, slow fatigue) motor units and a reduction in the contribution of type 2b units to the total frequency spectrum is reflected in a shift towards lower frequencies in addition to a decrease in total power. We suggest that a similar interpretation may be applied to the shift towards the lower frequencies contained in the ECAP during neuromuscular blockade by atracurium and vecuronium.

There is good evidence that the different types of muscle fibre are not equally affected by neuromuscular blocking drugs. Day and colleagues (1983) have demonstrated, in the cat, preferential blockade of fast (gastrocnemius) fibres compared with slow (soleus) fibres by tubocurarine. In contrast, in a volunteer study, Secher, Rube and Secher (1982) found that the EMG activity in maximally contracting muscle was reduced by a small dose of tubocurarine to a greater extent in soleus (71% slow fibres) compared with gastrocnemius (54% slow fibres). Although there were considerable methodological differences between the studies, the apparently opposing findings suggest that there are interspecies differences in the relative susceptibility of fast and slow fibres. Further investigation is necessary to establish the importance of muscle fibre type in the development of neuromuscular blockade in man.

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RECOVERY OF RESPIRATION AFTER NEUROMUSCULAR BLOCKADE WITH ALCURONIUM

B. A. ASTLEY, R. HUGHES AND J. P. PAYNE

SUMMARY

Alcuronium 0.2 mg kg^{-1} was given to six patients to investigate the simultaneous recovery of breathing and peripheral neuromuscular function. Anaesthesia was maintained with 66% nitrous oxide in oxygen supplemented with 0.5% halothane, and the patients were ventilated to normocarbia. Patients were disconnected from the ventilator after the reappearance of the tetanic response. This response returned at a mean time of 19.2 min after the injection of alcuronium and oxygenation was maintained thereafter by means of apnoeic diffusion. Spontaneous breathing returned at a mean time of 23.6 min after the injection of alcuronium. Sixty minutes after the administration of alcuronium, respiratory exchange was judged adequate, and at that time neuromuscular function was still markedly depressed with a tetanic height less than 25% of control. It was concluded that, because of the slow recovery of neuromuscular function, alcuronium should be reserved for the longer surgical procedure.

Since its introduction in 1961, it has been widely held that the action of alcuronium is of medium duration, and is readily reversed. In the absence of the regular monitoring of neuromuscular transmission, such a conclusion must have been based on clinical observation, presumably based on tests such as head raising, handgrip strength or the adequacy or otherwise of respiration. However, it is well known that competitive neuromuscular blocking agents tend to have a relatively sparing effect on respiratory muscles as compared with peripheral muscles (Foldes et al., 1961; Johansen, Jorgensen and Molbech, 1964; Ali et al., 1975; Gal and Smith, 1976; Wymore and Eisele, 1978), so that the duration of action may seem shorter than it actually is. Accordingly, it was decided to compare the recovery of respiration with that in the small muscles of the hand in a group of anaesthetized patients after the administration of alcuronium.

PATIENTS AND METHODS

Six unpremedicated patients who were about to undergo urological surgery gave their informed consent to the study. The patients were fit men with an average age of 45.8 yr (range 18–59 yr).

Anaesthesia was induced with 5% thiopentone 400–600 mg i.v. given into a fast flowing infusion in a vein on the forearm, and maintained with 60–66% nitrous oxide in oxygen supplemented with 0.5% halothane plus increments of thiopentone as necessary. Tidal volume was measured with a Wright's respirometer and the respiratory pattern recorded by means of a thermistor placed in the catheter mount. End-tidal carbon dioxide concentration was measured with a capnograph (Datex). Heart rate and rhythm were monitored throughout each study. A polyethylene cannula was inserted to a radial artery (usually the left) to permit the continuous measurement of arterial pressure, and the regular collection of blood samples.

Simultaneous recordings of tetanic and single twitch contractions of the adductor pollicis muscles were obtained by stimulating each ulnar nerve supramaximally at the wrist every 12 s, one

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TABLE I. *Time course of neuromuscular block and initial recovery*

Patients	Complete block of tetanus (s)	Time to intubation (min)	Complete block of twitch (min)	Return of twitch (min)	Return of tetanus (min)	Return of spontaneous respiration (min)
1	42	2.0	3.0	47	27	32
2	40	2.7	4.3	14	17	19
3	65	1.5	5.0	18	11	19
4	39	2.0	9.2	21	25	26
5	40	2.0	6.8	14	14	20
6	42	2.0	3.0	18	21	25.5
Mean	45	2.0	5.2	22	19.2	23.6
SEM	±4.1	±0.17	±0.98	±5.1	±2.6	±2.1

TABLE II. *Respiratory and blood-gas values*

	Tidal volume (ml)	End-tidal CO_2 (%)	pH range	P_{CO_2} (kPa)	P_{O_2} (kPa)
Control	257.0±29.6	Not measured	7.26–7.45	7.08±0.59	20.9±2.08
On ventilator	800	4.63±0.47	7.35–7.49	5.10±0.33	21.6±1.97
5 min off	204±41.0	6.17±0.49	7.25–7.37	7.42±0.49	24.6±2.74
15 min off	258.3±30.7	7.08±0.61	7.17–7.37	7.40±0.73	23.0±1.81
30 min off	323.3±19.6	6.25±0.53	7.21–7.38	7.02±0.57	21.8±1.86
60 min off	336.7±24.6	6.17±0.60	7.31–7.39	6.34±0.35	18.9±2.22
After reversal	343.7±12.8	5.53±0.46	7.32–7.35	6.17±0.33	19.0±2.28

with tetanic bursts of 50 Hz for 1 s, and the other with single shocks of 0.1 ms duration. After baseline recordings (which served as controls) were obtained, alcuronium 0.2 mg kg^{-1} was given as an i.v. bolus, the trachea was intubated and artificial ventilation commenced. The minute volume was adjusted to give an end-tidal carbon dioxide concentration of between 4 and 6%. Artificial ventilation was continued until the reappearance of the tetanic response, at which point it was discontinued and oxygenation maintained thereafter by means of the apnoeic diffusion technique first described by Enghoff, Holmdahl and Risholm (1951).

The return of spontaneous breathing was recorded and its adequacy assessed by serial measurements of tidal volume and end-tidal carbon dioxide concentration. In addition, arterial blood samples were taken at 5, 15, 30 and 60 min after the return of spontaneous breathing for subsequent analysis. Because of the slow recovery of neuromuscular function it was necessary to administer neostigmine (preceded by atropine 1.2 mg) i.v. These drugs were given at varying arbitrary times which depended upon the time available to complete each study. Results were expressed as the means ± SEM.

RESULTS

The mean times of onset of, and initial recovery from, neuromuscular blockade (measured from the administration of alcuronium) are shown in table I. Complete blockade of the tetanic response occurred very quickly—in a mean time of 45±4.1 s; blockade of the twitch response occurred more slowly at 5.22±0.98 min after the administration of the drug. The tetanic response returned at 19.2±2.6 min, after which patients were disconnected from the ventilator. Spontaneous breathing returned 23.6±2.1 min after the injection of the drug.

The results of the serial tidal volume and end-tidal carbon dioxide measurements, together with those of the arterial blood analyses, are shown in table II. Mean values demonstrate a gradual increase with time in tidal volume—from 204±4.1 ml at 5 min, to 343±12.8 ml after antagonism, and the simultaneous decrease in arterial carbon dioxide partial pressures from 7.42±0.49 kPa at 5 min to 6.17±0.23 kPa after antagonism. The values of end-tidal carbon dioxide concentration mirrored the arterial carbon dioxide tensions. Thirty minutes after the onset of spontaneous respiration, that is, approximately

TABLE III. *Degree of blockade 60 min after injection of alcuronium*

Patients	Twitch height (% of control)	Peak tetanic height (% of control)	Degree of tetanic fade (%)
1	15.6	18.9	87.5
2	53.8	35.5	77.8
3	13.0	21.8	87.5
4	34.5	12.9	100.0
5	96.4	41.0	76.0
6	19.3	15.6	92.0
Mean ± SEM	38.76 ± 13.09	24.0 ± 4.6	87.0 ± 3.7

60 min after the alcuronium had been given, mean tidal volume was 323.3 ± 19.6 ml, end-tidal carbon dioxide partial pressure 6.25 ± 0.5% and Pa_{CO_2} 7.02 ± 0.57 kPa. These compare favourably with the control values.

The degree of residual neuromuscular blockade at 60 min after the administration of the alcuronium is shown in table III. The values quoted for tetanic fade were calculated as the difference between the peak height of the tetanic contraction and that of the sustained contraction expressed as a percentage of the peak height. Despite adequate respiratory exchange, the degree of blockade (at approximately 60 min) was substantial; the peak height of the twitch contraction was 38.76 ± 13.09% of control and the peak height of the tetanic contraction had only recovered to a mean of 24 ± 4.6% of control with 87 ± 3.7% fade (table III).

Table IV shows the times (min) of administration of neostigmine, measured from the injection of the alcuronium, the degree of recovery present at antagonism and the time taken from the injection of neostigmine to 95% recovery of the twitch and tetanic heights. Neostigmine was given 73–120 min after the alcuronium. Before antagonism, the twitch response ranged from 45 to 100% of control, and the recovery of the tetanic response ranged from 28 to 58% of control peak height with 86–25% fade. After antagonism, 95% recovery of the twitch response was achieved within 1–6 min, and 95% recovery of the tetanic response within 9 min for five patients. However, in the sixth patient, the tetanic height reached only 56% of control after one dose of neostigmine and a second dose was given, bringing tetanic height to 75% of control. The pattern of recovery followed the degree of blockade present when neostigmine was given. The patient with the greatest degree of spontaneous recovery (tetanic height 58% of control) recovered the fastest and the patient with the least recovery (tetanic height 18% of control) was the slowest to recover from the neuromuscular blockade.

DISCUSSION

In this study, respiratory exchange was finally judged to be adequate 60 min after the administration of alcuronium. At this stage peripheral neuromuscular function was still markedly depressed with a mean tetanic height of 24 ± 4.6% of control and with 87 ± 3.7% fade. This study, therefore, demonstrated the respiratory sparing effect of alcuronium in anaesthetized man. The long duration of action of alcuronium explains the occasionally disappointing antagonism of its action following neostigmine. If recovery is required after a short procedure such as laparoscopy (lasting 20 min), antagonism may be unsatisfactory at this stage as spontaneous recovery is just beginning to occur and antagonism from

TABLE IV. *Effect of neostigmine on recovery process.* **This patient was given two doses of neostigmine. The first dose increased tetanic height to 56% of control height, and the second dose to 75% of control*

Patient	Time from alcuronium administration to injection of neostigmine (min)	Degree of recovery at injection of neostigmine		Time taken from neostigmine injection to recovery of	
		Twitch height (% control)	Tetanic height (% control)	Twitch height (95%) (min)	Tetanic height (95%) (min)
1	94	53	41	3.0	4.5
2	99	84.6	55.0	1.0	3.0
3	73	23	28	7.5	9.0
4	84	53	18	4.0	*
5	120	100	58	0.0	1.0
6	94	45	33	6.0	6.0

minimal recovery is unreliable (Katz, 1967). In this study we did not give neostigmine at a predetermined point in the return of neuromuscular function, as the effects of neostigmine were not being examined.

Other workers have found a long duration of action with alcuronium. On clinical grounds, Hunter (1964) concluded that alcuronium had a fairly "short action", but that antagonism with neostigmine was unreliable. Baraka (1967) found no difference in the duration of action between alcuronium and tubocurarine. Heneghan, McAuliffe and Radford (1981) compared two techniques of tracheal anaesthesia for dental surgery. One group of patients were allowed to breathe oxygen, nitrous oxide and halothane spontaneously, while the other group were ventilated mechanically after neuromuscular blockade with alcuronium. The latter technique was associated with a significantly higher incidence of morbidity. At discharge, 17 of 24 patients in the alcuronium group had double vision (halothane group 0), and 23 of 24 in the group who had received a neuromuscular blocker felt weak compared with 14 in the halothane group. More recently Collins, Plantevin and Docherty (1984) compared the use of atracurium and alcuronium in day-case gynaecological surgery and noted a marked decrease in minor postoperative sequelae in the atracurium group, which they attributed to the shorter duration of atracurium. Lin and Homi (1985) concluded, as a result of their comparison of alcuronium with atracurium, that alcuronium had a long duration of action.

Like other general anaesthetics halothane, in sufficient concentration, will cause muscle relaxation which results primarily from depression of the central nervous system (Ngai, Hanks and Farhie, 1965). It is also well established that halothane enhances and prolongs the paralysing effects of competitive blocking agents (Katz and Gissen, 1967; Hughes and Payne, 1979). Hughes and Payne (1979) found no effect on a 50-Hz tetanus in the presence of 1 and 2% halothane before the administration of tubocurarine, dimethyltubocurarine and gallamine, but found increased tetanic fade and decreased peak tetanic height after the administration of these drugs. These workers have not demonstrated a significant effect with halothane in concentrations less than 1%. More recently Hackett, Hughes and Payne (1983) have shown no difference in recovery times following neuromuscular blockade with atracurium in patients anaesthetized with etomidate or halothane. Therefore, we have assumed that the presence of 0.5% halothane did not significantly influence recovery in this study.

There is at present no clinical test to determine whether all receptors are free of neuromuscular blocker and we do not know how sensitive a test must be to ensure adequate muscle strength to overcome airway obstruction and permit effective coughing. A normal response to a 50-Hz tetanus predicts that responses to physiological frequencies are unimpaired, but does not estimate the fraction of receptors in excess of those required for normal transmission, that is the margin of safety which is narrowed by anaesthesia and partial curarization (Waud and Waud, 1972). Harrison (1978), in a retrospective survey of deaths attributable to anaesthesia, points out that respiratory inadequacy following myoneural blockade was the second commonest cause of mortality after hypovolaemia. Respiratory exchange was shown to be adequate in the present study, in fit patients with tracheal tubes *in situ* to guarantee the patency of the airway, in the presence of a much reduced tetanic response with marked tetanic fade of the adductor pollicis muscle. In view of its delayed recovery characteristics, it is suggested that alcuronium be reserved for the longer surgical procedure. Furthermore, since this study has demonstrated that adequate respiration is not a reliable index of recovery, it is advisable to assess neuromuscular function with a peripheral nerve stimulator before and after induced reversal with neostigmine.

ADDENDUM

Onset of recovery of the twitch response usually precedes that of the tetanic contraction, but in this study the recordings did not conform to this pattern (table II). In an attempt to eliminate electrical interference from the twitch recording, a suppression unit had been incorporated to the circuitry and had the effect of damping the initial weak responses. Consequently, the apparent recovery of the twitch responses was delayed and therefore these values are inaccurate.

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CLINICAL EXPERIENCE AND PLASMA LAUDANOSINE CONCENTRATIONS DURING THE INFUSION OF ATRACURIUM IN THE INTENSIVE THERAPY UNIT

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SUMMARY

Twenty patients in the intensive care unit received an infusion of atracurium to permit mechanical ventilation. The duration of infusion ranged from 38 to 219 h and the average rate of infusion during the study was 0.76 mg kg^{-1} h^{-1}. In 14 patients an increase in atracurium requirement occurred within the first 72 h of the infusion. Recovery from neuromuscular blockade after a prolonged infusion was sufficiently rapid to avoid pharmacologically induced reversal. In six patients maximum plasma concentrations of laudanosine were 1.9–5 μg ml^{-1}, and there was no evidence of cerebral excitation.

The use of neuromuscular blockade in the intensive therapy unit (ITU) is controversial: many clinicians are concerned about the risk of awareness when the patient is paralysed, and of accidental disconnection from the ventilator (Willatts, 1985). However, there is evidence which suggests that neuromuscular blockade may be beneficial in the management of certain conditions, notably adult and neonatal respiratory distress syndrome (Pollitzer et al., 1981; Greenough et al., 1984), tetanus (Edmondson and Flowers, 1979) and head injury (McDowall, 1983). Surveys of intensive therapy units suggest that the use of neuromuscular blocking agents is widespread (Miller-Jones and Williams, 1980; Merriman, 1981). However, there are very few data on the appropriateness of the individual agents in the ITU, and choices have been based largely on experience gained in the operating theatre.

The requirements for the ideal drug would include good cardiovascular stability, lack of histamine release, no cumulation, and a means of elimination which is independent of hepatic and renal function. It is important that the neuromuscular blockade can be antagonized easily and rapidly when required, to permit assessment of the patient and for weaning from mechanical ventilation—even in the presence of multiple organ failure. In addition, the drug should be suitable for administration by infusion, a technique that offers the advantage of convenience and avoids the need for i.v. bolus doses which may be associated with serious cardiovascular- and histamine-related effects (Scott et al., 1985). Atracurium, a relatively new competitive neuromuscular blocking agent of intermediate duration, would appear to have many of these features. It has been used successfully by infusion for prolonged surgery (Eagar, Flynn and Hughes, 1984; Gargarian et al., 1984). Thus it would seem appropriate to extend investigation of this agent into the ITU. There are already several case reports of the use of atracurium in the ITU (Hutchinson and Pinnock, 1984; Powles and Ganata, 1985; Thomas and Windsor, 1985); in addition, there are reports of infusions of up to 22 days' duration (Wadon, Dorga and Anand, 1986). However, the unique metabolism of atracurium has given rise to new anxieties: in particular, concern has been expressed regarding possible seizure activity caused by laudanosine, a product of both the Hofmann degradation and ester hydrolysis of atracurium (Hennis et al., 1984).

The aim of this investigation was twofold; first

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a dose-finding study and, second, to make serial measurements of plasma laudanosine concentrations during the infusion of atracurium in the ITU.

PATIENTS AND METHODS

Twenty patients admitted to our ITU who required the administration of neuromuscular blocking agents (to facilitate satisfactory intermittent positive pressure ventilation (IPPV)) were entered to the trial. Ethical committee approval and informed consent from the patients' next-of-kin were obtained.

An infusion of undiluted atracurium solution 10 mg ml^{-1} was delivered from a 50-ml syringe driven by a Treonic IP3 Syringe Pump (Vickers). The infusion was commenced at a rate of 0.4 mg kg^{-1} h^{-1} and then adjusted by the clinical staff of the ITU to provide good conditions for IPPV. All patients received regular doses of midazolam 2.5 mg i.v. supplemented in some cases by phenoperidine 1–2 mg to provide sedation and analgesia. At regular intervals, neuromuscular transmission was allowed to recover spontaneously to permit neurological assessment. No attempt was made to achieve any fixed degree of neuromuscular blockade, although some moni-

TABLE I. *Patient details, infusion rates, duration of infusion and diagnoses. †Plasma laudanosine concentrations measured.* **Renal failure*

Initials	Age (yr)	Sex	Weight (kg)	Duration of infusion (min)	Dose (mg kg^{-1})	Mean infusion rate (mg kg^{-1} h^{-1})	Max. infusion rate (mg kg^{-1} h^{-1})	Diagnosis on admission
A.B.	68	F	50	124	103	0.83	1.00	Multiple injuries Respiratory failure
B.B.	32	M	80	219	130	0.59	0.88	Head injury
P.P.	52	M	60	195	131	0.68	1.0	Head injury
R.I.	19	M	80	92	108	1.17	1.6	Head injury
R.J.	17	M	70	176	214	1.22	1.57	Head injury Chest injury
A.S.	24	M	70	162	141	0.87	1.07	Head injury
B.S.	52	M	60	147	94	0.64	0.83	Septicaemia*
M.U.	50	M	70	93	71	0.77	1.1	Head injury
D.K.	38	M	64	71	57	0.8	0.94	Acute myeloid leukaemia Septicaemia*
D.J.	17	M	70	181	178	0.98	1.45	Septicaemia Hepatocellular jaundice*
H.R.	20	F	60	180	78	0.42	0.5	Bone marrow transplant*
R.M.	66	M	65	48	22	0.46	0.46	Pulmonary fibrosis Pseudomonas pneumonia*
A.B.	8	M	35	120	60	0.5	0.57	Head injury Fractured femur
C.N.	50	M	80	128	58	0.45	0.62	Cardiac failure ARDS*
V.B.†	68	F	50	110	69	0.63	0.8	Multiple injuries Respiratory failure
R.S.†	64	M	70	139	110	0.79	0.86	Cardiac failure
G.S.†	24	M	70	38	43	1.1	1.43	Head injury
C.P.†	44	M	80	124	112	0.9	1.0	Acute pancreatitis* Obstructive jaundice
A.M.†	65	M	70	40	24	0.61	0.71	Abdominal aortic graft*
B.C.†	58	M	70	113	83	0.73	0.87	Faecal peritonitis Respiratory failure*

toring was performed by assessment of the response of the muscles of the hand to train-of-four stimulation of the ulnar nerve, either by visual inspection or by recording the evoked electromyogram (Datex Relaxograph).

Blood samples were taken in six patients before the commencement of the infusion, and during the infusion, for estimation of plasma laudanosine and atracurium concentrations. Immediately after collection the samples were centrifuged in a high speed centrifuge, 0.2 ml of the plasma was mixed with 0.8 ml of sulphuric acid 0.015 mol litre^{-1} and frozen. Samples were later analysed by high pressure liquid chromatography (Simmonds, 1985).

Statistical tests were used where appropriate as specified in the text and results are expressed as mean values ± SEM with ranges.

RESULTS

Twenty patients (mean age 41 ± 4.5 yr and mean weight 66 ± 2.5 kg) requiring prolonged artificial ventilation were studied. Patient characteristics, together with doses of atracurium, infusion rates, duration of infusion and diagnoses are given in table I. Eight patients were in renal failure and were undergoing haemodialysis.

The average infusion rate throughout the study was 0.76 ± 0.05 mg kg^{-1} h^{-1} (range 0.45–1.22). The mean infusion rate over the first 12 h was 0.48 ± 0.03 mg kg^{-1} h^{-1}. In most patients an increase in atracurium requirement occurred within the first 72 h of infusion as indicated in figure 1 (mean rate at 72 h 0.76 ± 0.06 mg kg^{-1} h^{-1}).

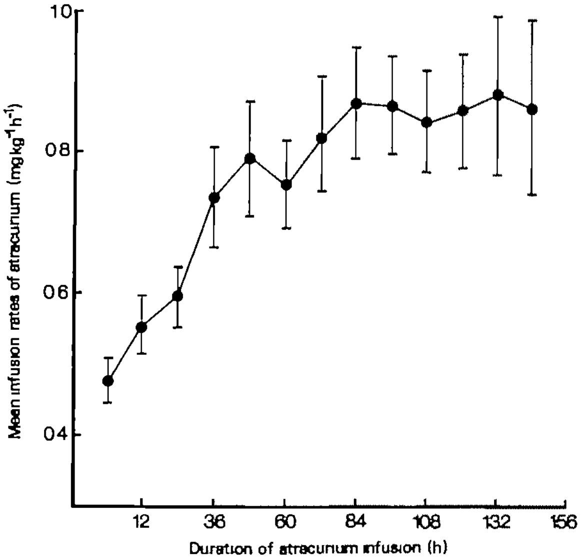

FIG. 1. Mean infusion rates ± SEM of atracurium required after various periods of infusion.

Statistical analysis (one-way analysis of variance) showed this increase to be significant ($P < 0.01$). This feature is also illustrated in figure 2, which shows segments of the recording of the evoked electromyogram from patient G. S. It can be seen that the degree of neuromuscular blockade achieved did not markedly change over the 38 h of infusion, despite the large increase in the rate of infusion. In addition, this stable level of blockade was associated with an increase in the plasma atracurium concentration from 1.5 µg ml^{-1} at 70 min to 5.3 µg ml^{-1} at 38 h. Another feature illustrated in figure 2 is the modest degree of neuromuscular blockade required to facilitate mechanical ventilation—a finding common to all the 20 patients studied. Despite wide changes in temperature (from 35 to 39 °C) and blood pH (from 7.2 to 7.5) during the infusions of atracurium, there was no significant correlation between changes in these variables and the increase in the infusion rate.

Details of recovery were not available for all the patients for a variety of reasons, including change to another neuromuscular blocking drug, satisfactory IPPV without neuromuscular blockade, and death. In eight patients the mean time from the end of the infusion to satisfactory spontaneous ventilation was 75 min (range 30–120 min) after infusions of a mean duration of 111 h. The decision to discontinue IPPV was not solely based on recovery from neuromuscular blockade, but was also determined by recovery from the sedative and analgesic agents used. In no patient was antagonism of neuromuscular blockade considered necessary.

The plasma concentrations of laudanosine in the six patients studied are shown in figure 3. The maximum laudanosine concentrations in each patient ranged from 1.9 to 5.1 µg ml^{-1} and there was an indication of a plateau after 2–3 days of infusion. The highest laudanosine concentration was found in patient R. S. who, at the time, had no biochemical evidence of serious hepatic or renal failure. The two patients with the highest concentrations (R. S. and B. C.) were weaned successfully from cardiovascular support. The decrease in concentration in patient V. B. was the result of a temporary cessation of the infusion.

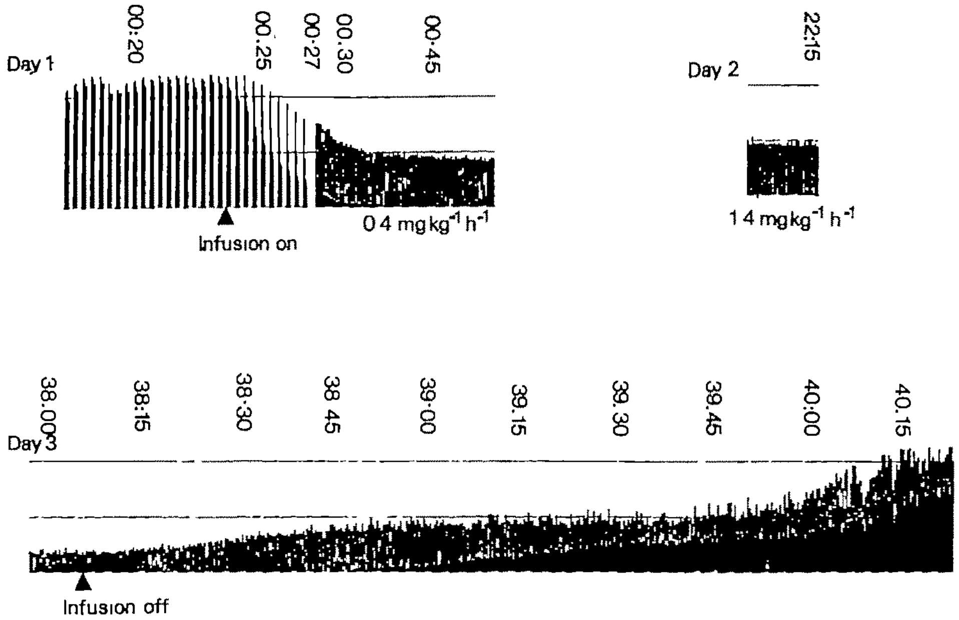

FIG. 2. Recording at fast and slow paper speeds of the electromyogram of the muscles of the hand in response to train-of-four stimulation of the ulnar nerve from patient G. S. who received an infusion of atracurium over 3 calendar days.

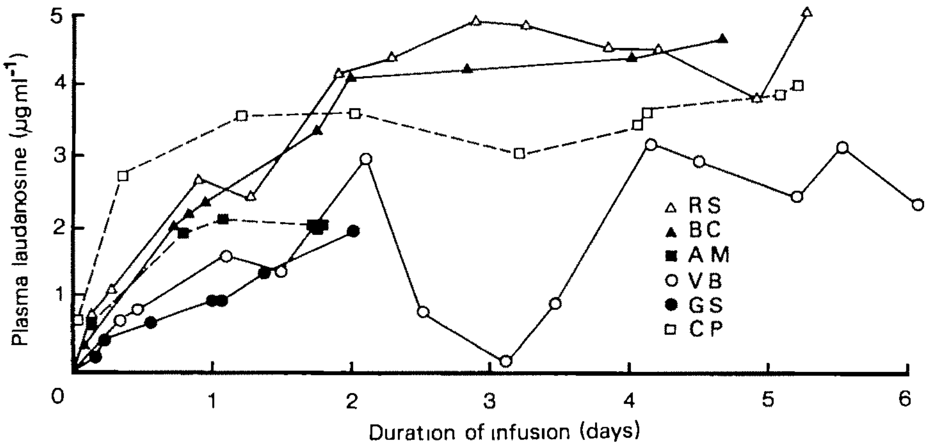

FIG. 3. Plasma laudanosine concentrations in six patients during atracurium infusion.

Two patients died while the atracurium infusion was in progress, and another seven patients died between 3 h and 18 days after the infusion was stopped. In no case was the clinical course surprising, and no death was attributed to the atracurium. In one patient, infusion of atracurium was discontinued prematurely when the patient developed a generalized erythematous rash; histological diagnosis subsequently identified the cause as infection. No other side effects were observed which were considered to be related to the atracurium, and the clinical impression was favorable.

There was no evidence of siezure activity in any patient, and it is unlikely that this would have been concealed by the neuromuscular blockade in view of the modest degree of blockade achieved. In two patients, electroencephalograms performed at days 5 and 6 of the infusions showed no evidence of cerebral excitation.

DISCUSSION

The average infusion rate (0.76 mg kg^{-1} h^{-1}) required to maintain relaxation in patients under sedation in the intensive care unit was substantially higher than that of 0.4 mg kg^{-1} h^{-1} used previously during a balanced anaesthetic technique for prolonged surgery (Eagar, Flynn and Hughes, 1984), but similar to that reported in a study of atracurium infusions in patients in renal failure on an ITU (Griffiths, Hunter and Jones, 1986). Although there was a tendency for the temperature and blood pH to increase in some patients during the infusion of atracurium, there was no correlation between the increase in infusion rate over the first 72 h of infusion and the changes in these variables. It seems unlikely, therefore, that it could be attributed to a more rapid breakdown of atracurium by "Hofmann elimination", a process which is dependent on temperature and pH. In addition, it is unlikely to be the result of the declining effect of recent anaesthesia, as none of these patients had received an anaesthetic for 2 days before the commencement of the infusion, and some not for more than 1 week. A possible explanation for this phenomenon is the development of resistance to atracurium, since a similar effect has been observed in cats after prolonged paralysis with tubocurarine (Matteo and Diaz, 1984), and in man with pancuronium (Callanan, 1985). The reason for this apparent decrease in sensitivity is uncertain, but it has long been known that denervation of skeletal muscle leads to supersensitivity to acetylcholine (Axelsson and Thesleff, 1959). In particular, Berg and Hall (1975) demonstrated increased extrajunctional acetylcholine sensitivity after the chronic administration of tubocurarine. Other possible reasons have been reviewed by Gronert (1986) and include: altered pharmacokinetics as a result of altered metabolism, distribution or excretion—this is not supported by the plasma atracurium concentrations in patient G.S., disuse atrophy (Gronert, 1981); drug interaction—as is in the nature of intensive care, many of these patients were receiving multiple drug therapy and the possibility of drug interaction cannot be discounted.

Of the currently available competitive neuromuscular blocking drugs, atracurium has the shortest elimination half-life and is, probably, the only agent the half-life of which is unaffected by hepatic or renal failure (Ward and Neill, 1983). It has been shown to be the least cumulative of the currently available drugs (Ali et al., 1983). In addition, atracurium has been demonstrated to have minimal cardiovascular effects (Hilgenberg, Stoelting and Harris, 1983), although it has been shown to provoke the release of small but significant amounts of histamine (Basta et al., 1983). Whether the theoretical pharmacokinetic advantages of atracurium over other competitive blockers can be demonstrated to have clinical advantages in the ITU is yet to be seen. Vecuronium has a very similar clinical profile but, as yet, there has been little experience of the drug in the ITU. Powles and Ganata (1985) reported a patient with tetanus who was treated initially with an atracurium infusion, but developed numerous episodes of bradycardia which resolved on changing to vecuronium. However, clinical experience gained during the present study showed no evidence of cardiovascular instability associated with atracurium.

Recently, the issue of the potential toxicity of the metabolites of this drug has been raised. This is especially important in the ITU where large doses of atracurium may be administered in the course of several days. One metabolite in particular, laudanosine, has caused concern. This compound has a substantially longer half-life (197 min (Ward et al., 1985)) than atracurium and could be expected to accumulate in an ITU setting. Laudanosine, a product also of morphine metabolism, has long been known to cause convulsions in high doses (Mercier and Mercier, 1955). A recent study (Chapple, Miller and Wheatley, 1985) identified the threshold for convulsions in dogs as 17 μg ml^{-1}. This plasma concentration may be significantly higher in man in view of the far lower cerebrospinal fluid:plasma ratios in man of 0–14% (Fahey et al., 1985) compared with those in the dog of 40–60% (Hennis et al., 1984). In our study we found a maximum plasma laudanosine concentration of 5.1 μg ml^{-1}. Although a small group of patients with a wide variety of pathology were studied, the plasma concentrations of laudanosine should give a reliable indication of the maximum concentration likely to be achieved. In fact, the plasma laudanosine concentrations in this study were in accordance with previous pharmacokinetic predictions for steady-state values (Ward et al., 1985). Thus it seems unlikely that concentrations of laudanosine great enough to provoke siezures will be reached. Of more importance is whether these concentrations could provoke more subtle changes which could be harmful to the critically ill patients. At clinical concentrations of atracurium a 30% increase in the minimum alveolar concentration of halothane was found in rabbits (Shi et al., 1985). Furthermore, electroencephalographic changes were found in cats at concentrations of laudanosine greater than 4.4 $\mu g\ ml^{-1}$ (Ingram et al., 1985). However, in studies with atracurium in dogs (Lanier, Milde and Mitchenfelder, 1985) and cats (Litwak et al., 1985), no effects could be detected on intracranial pressure, cerebral blood flow or cerebral metabolic rate for oxygen.

In conclusion, data were collected from 20 patients receiving an infusion of atracurium for a prolonged period in the ITU. There was an impression of increasing drug requirement with time. The clinical impression gained was favorable. Maximum plasma laudanosine concentrations (measured in six patients) gave a range of 1.9–5.1 $\mu g\ ml^{-1}$, substantially below concentrations required to cause seizures in dogs. Further information is required on the effects of these concentrations in man and any concern raised by these figures should be balanced against the extensive clinical experience with this drug.

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CARDIOVASCULAR AND NEUROLOGICAL EFFECTS OF LAUDANOSINE

Studies in Mice and Rats, and in Conscious and Anaesthetized Dogs

D. J. CHAPPLE, A. A. MILLER, J. B. WARD AND P. L. WHEATLEY

Atracurium, a novel competitive neuromuscular blocking agent, is metabolized in animals (Neill and Chapple, 1982; Neill, Chapple and Thompson, 1983) and man (Fahey et al., 1984) by non-enzymatic Hofmann elimination and by ester hydrolysis. Studies in animals have demonstrated that the products of these reactions produced no significant neuromuscular or cardiovascular effects at doses up to 2–4 mg kg^{-1} i.v. (Chapple and Clark, 1983). More recent clinical studies have demonstrated the presence of one of these metabolites, laudanosine, in detectable concentrations in human plasma (Fahey et al., 1984; Boheimer et al., 1984). Since the rapid bolus injection of laudanosine produces seizure activity in a variety of animal species (Babel, 1899; Mercier and Mercier, 1955), these observations led to concern that, during the administration of atracurium (either by bolus injection or by infusion), convulsant concentrations of laudanosine might be produced in man.

To model this situation we have studied the effects of infusions of laudanosine on the behaviour of conscious dogs and on the electroencephalogram (EEG) of dogs anaesthetized with halothane. We have attempted to correlate laudanosine plasma concentrations with the behavioural and EEG changes observed in these animals. In addition, we have studied the convulsant effects of the acute bolus administration of laudanosine in mice and rats, and the effects of pretreatment with some anticonvulsant drugs on laudanosine-induced seizures in rats.

A preliminary account of this work was presented at a meeting of the American Society of Anesthesiologists (Chapple et al., 1985).

SUMMARY

The effects of laudanosine, a metabolite of atracurium, on the behaviour of conscious mice, rats and dogs, and on cardiovascular function in conscious and anaesthetized dogs have been evaluated: EEG studies were performed in anaesthetized dogs. In mice and rats, i.v. bolus doses of laudanosine 10–20 mg kg^{-1}, caused convulsions and hind limb extensions; these effects were prevented by pretreatment with diazepam. After the continuous infusion of laudanosine to conscious dogs, plasma concentrations in the order of 1.2 μg ml^{-1} did not cause behavioural disturbances. In anaesthetized dogs, laudanosine plasma concentrations of more than 6 μg ml^{-1} caused hypotension and bradycardia, laudanosine concentrations greater than 10 μg ml^{-1} induced epileptic EEG spiking and plasma concentrations greater than 17 μg ml^{-1} produced prolonged seizures. There is a wide difference between laudanosine plasma concentrations in patients given atracurium by bolus injection or by short-term infusion for surgical use and those required to induce epileptic activity in dogs. However, during the prolonged infusion of atracurium to patients this difference will be decreased. It is unlikely that the use of atracurium, in patients, would result in plasma concentrations of laudanosine capable of producing neurological or cardiovascular disturbances.

MATERIALS AND METHODS

Mice and rats

Studies were undertaken using male CFLP mice weighing 18–25 g, and male Wistar rats weighing 120–150 g. Laudanosine was given i.v. to a tail vein, in a range of doses (5–20 mg kg^{-1}); the dose volumes used were 20 ml kg^{-1} for mice

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and 5 ml kg^{-1} for rats, resulting in similar final volumes for injection of 0.4–0.7 ml. The numbers of animals exhibiting convulsions and hind-limb extension were recorded.

The effect of oral pretreatment with standard anticonvulsant drugs on laudanosine-induced convulsions was studied in rats. Ethosuximide 640 mg kg^{-1}, sodium valproate 480 mg kg^{-1} and diazepam 34 mg kg^{-1} were administered 1 h before, and phenytoin 88 mg kg^{-1} and phenobarbitone 16 mg kg^{-1} were administered 2 h before, laudanosine 14 mg kg^{-1} i.v. The doses of sodium valproate, phenytoin, phenobarbitone and diazepam used were $2 \times ED_{50}$ the values which would, at the times selected, abolish hind-limb extension in rats using the maximum electroshock test (a standard test procedure for the evaluation of anticonvulsant drugs). Ethosuximide is ineffective in the electroshock test and was examined at a dose known to be effective against leptazol-induced convulsions. An ED_{50} for the abolition of hind-limb extension by diazepam was determined in mice. The diazepam was given orally before laudanosine 20 mg kg^{-1} i.v.

Conscious dogs

Four beagle dogs (two female; initial weight 10.7–11.2 kg) were trained to sit quietly in restraint slings within the laboratory. The electrocardiogram (ECG Lead II) was recorded continuously using subdermal needle electrodes and a Beckman type RM Dynograph recorder. Heart rate was measured at intervals by counting R waves over 6–10 s.

An i.v. catheter (Bardi-l-catheter) was inserted to a cephalic vein for the administration of laudanosine and another catheter inserted to a saphenous vein to obtain blood samples for the measurement of plasma drug concentrations.

In the initial study, laudanosine 2 mg kg^{-1} was given as an i.v. bolus. One week later, two of these dogs received an i.v. infusion of laudanosine 7.8 mg kg^{-1} h^{-1} for 30 min immediately followed by 2.04 mg kg^{-1} h^{-1} for 210 min. Behavioural observations were made throughout.

Anaesthetized dogs

In three beagle dogs (weighing 8.2–9.3 kg) anaesthesia was induced with thiopentone 20 mg kg^{-1} i.v. and, after cannulation of the trachea, was maintained with 0.5–1% halothane in oxygen 6 litre min^{-1}. Arterial pressure was measured from the left femoral artery with a fluid-filled catheter attached to a pressure transducer. The ECG (Lead II) was recorded continuously using subdermal needle electrodes. Heart rate was measured at intervals by counting R waves over 6–10 s.

The right femoral artery was cannulated to allow sampling of arterial blood for measurement of blood-gas tensions and pH, and for the determination of plasma concentrations of laudanosine. The right femoral vein was cannulated for the i.v. infusion of the drug.

To allow recording of the (EEG), a longitudinal incision was made in the scalp, and the skin and underlying tissues reflected to expose the skull surface. Burr holes (size 8) were made in the skull in the regions of the nasal sinus and overlying the left and right fronto–parietal cortices, left and right parietal cortices, right parieto–occipital cortex and left temporo–parietal cortex. Screw electrodes (12-mm, 8BA stainless steel) were inserted to the burr holes and connected to a Grass model 7P EEG/polygraph by soldered leads. Six monopolar EEG derivations, using the nasal electrode as the reference, were recorded continuously together with arterial pressure and the ECG, from 1 h before beginning the laudanosine infusion. All three dogs received a constant infusion of laudanosine 15.7 mg kg^{-1} h^{-1} until convulsions were observed.

Blood sampling and analysis

In each dog study 1-ml samples of venous or arterial blood, as appropriate, were taken at intervals throughout the experiment and placed in heparinized tubes. After centrifugation, plasma concentrations of laudanosine were measured using an HPLC technique (Simmonds, 1985).

Data analysis

Heart rate and, when recorded, arterial pressure were measured at intervals. Where possible mean ±SEM were calculated for a group of animals. The significance of any difference as a result of treatment with laudanosine was assessed by paired *t* test, using the figures obtained immediately before the dose or infusion (time 0) as controls. EEG records were analysed visually for changes from the control record, particularly for the appearance of sharp waves and epileptic spikes.

Drugs

Laudanosine (Aldrich Chemical Co. Ltd) was prepared by adding a volume of saline (10–20 ml), then acidifying slowly with hydrochloric acid 1 mol litre^{-1} to dissolve the drug. The solution was buffered to pH 7 with sodium bicarbonate 1 mol litre^{-1} and final concentrations (20–50 mg ml^{-1}) achieved by addition of the required amount of saline.

Solutions of ethosuximide (Parke–Davis), sodium valproate (Labaz), and phenobarbitone sodium (British Drug House), were made up in normal saline. Diazepam (Roche) and phenytoin sodium (Sigma) were prepared as suspensions in a methyl cellulose suspension (0.25% in distilled water). Injectable diazepam was used for i.v. administration in anaesthetized dogs.

RESULTS

Mice and rats

In mice, bolus doses of laudanosine, 5 and 10 mg kg^{-1} i.v. ($n = 10$ per dose), did not produce convulsions, whereas greater doses, 15 and 20 mg kg^{-1}, induced behavioural convulsions in all mice tested ($n = 6$ and 16, respectively) with hind-limb extension in three out of six and 14 out of 16 mice, respectively.

In rats, laudanosine 5 and 7 mg kg^{-1} i.v. did not produce convulsions ($n = 7$ and 4, respectively), whereas doses of 14 and 20 mg kg^{-1} induced behavioural convulsions and hind-limb extension in all rats tested ($n = 4$ and 3, respectively.) At 10 mg kg^{-1}, six of the nine rats studied convulsed with hind-limb extension in two of the nine.

TABLE I. *Mean plasma concentrations (± SEM) after (a) a bolus dose of laudanosine 2 mg kg^{-1} i.v. in four conscious dogs, and (b) during and after an infusion of laudanosine 7.8 mg kg^{-1} h^{-1} for 30 min and then 2.04 mg kg^{-1} h^{-1} for 210 min in two conscious dogs.* n = *Number of dogs;* *n = *3*

(a) $n = 4$		(b) $n = 2$		
Time (min)	Laudanosine (μg ml^{-1})	Time (min)	Laudanosine (μg ml^{-1})	
			Dog 1	Dog 2
1.5	1.07 ± 0.19*	30	1.25	1.17
3	1.05 ± 0.18	60	1.19	1.24
5	0.88 ± 0.16	120	1.01	1.24
10	0.82 ± 0.17	180	1.06	1.35
20	0.66 ± 0.08	240	1.09	1.42
40	0.40 ± 0.05	Infusion off		
75	0.20 ± 0.02	1.5	1.35	1.49
150	0.09 ± 0.017	3	1.33	1.32
240	0.028 ± 0.005	5	1.27	1.33
420	0.005 ± 0.0047	10	0.98	1.32
24h	0.001 ± 0.001	20	0.88	1.20
		40	0.79	1.12
		60	0.67	0.87

Interaction studies. The dose of laudanosine selected for the anticonvulsant interaction studies was 14 mg kg^{-1}, the lowest dose which induced both behavioural convulsions and hind-limb extension in all rats tested. In the interaction studies an additional 10 rats received laudanosine 14 mg kg^{-1}; all convulsed and only one rat failed to show hind-limb extension. In rats, pretreatment with doses (by mouth) of ethosuximide 640 mg kg^{-1}, sodium valproate 480 mg kg^{-1}, phenytoin 88 mg kg^{-1} and phenobarbitone sodium 16 mg kg^{-1} did not prevent hind-limb extension or convulsive activity ($n = 4$ or 6 per treatment group). Diazepam 34 mg kg^{-1} by mouth ($n = 4$) caused complete inhibition of the convulsant activity of laudanosine 14 mg kg^{-1} i.v.

An ED_{50} for diazepam 2.1 mg kg^{-1} (by mouth) was measured in mice for the abolition of hind-limb extension, a dose closer to the therapeutic range than that administered to rats.

Conscious dogs

Bolus doses of laudanosine 2 mg kg^{-1} i.v. produced some agitation in two of the four dogs 4 min after the drug and was associated with plasma concentrations of laudanosine of 0.88 ± 0.16 μg ml^{-1}. Salivation occurred in three of the four dogs 4–60 min after administration; in the fourth, licking of lips was observed. Heart rate increased by 41 ± 10.2 beat min^{-1} within 1 min and recovery was not complete until 75 min had elapsed. Plasma concentrations of laudanosine were 1.07 ± 0.19 μg ml^{-1} at 1.5 min after administration and decreased exponentially over the next 420 min (table I).

The infusion of laudanosine 7.8 mg kg^{-1} h^{-1} for 30 min followed immediately by an infusion of laudanosine 2.04 mg kg^{-1} h^{-1} for 210 min produced no behavioural effects. Salivation occurred at 35 and 45 min after the start of the laudanosine infusion. Heart rate was increased by 50 and 40 beat min^{-1}, 45 and 60 min, respectively, after the commencement of the laudanosine infusion. Infusion of laudanosine 7.8 mg kg^{-1} h^{-1} for 30 min produced plasma concentrations of 1.21 μg ml^{-1}. This concentration was maintained for the next 210 min by an infusion rate of 2.04 mg kg^{-1} h^{-1}. The mean plasma concentration was 1.26 μg ml^{-1} at the end of the infusion (table I).

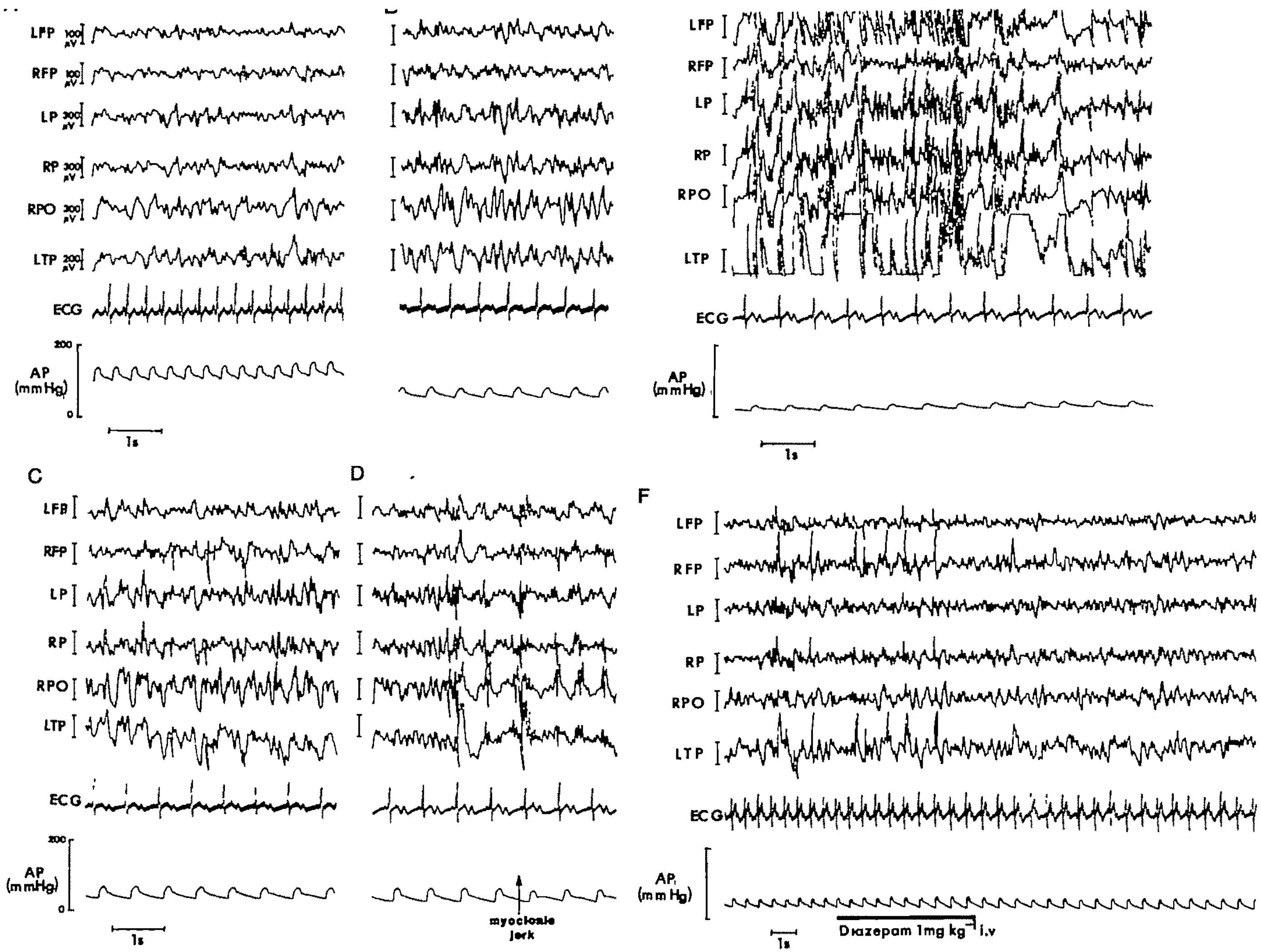

FIG. 1. Samples from a single dog of cortical EEG, AP and ECG recordings. A: Control; B: 60 min; C: 120 min; D: 170 min; E: 180 min after the start of an i.v. infusion of laudanosine 15.7 mg kg^{-1} h^{-1}. Trace F: was taken 7 min after E at the time of a second i.v. injection of diazepam 1 mg kg^{-1}. Note the increase in EEG amplitude and frequency at B, the appearance of spiking at C and the appearance of polyspikes accompanied by myoclonic jerks at D. At E the animal was in a behavioural clonus. The injection of diazepam 1 mg kg^{-1} abolished the seizure activity and the second injection at F normalized the EEG. EEG calibration bars in A are in µV and apply to all subsequent recordings. LFP = left fronto–parietal cortex; RFP = right fronto–parietal cortex; LP = left parietal cortex; RP = right parietal cortex; RPO = right parieto–occipital cortex; LTP = Left tempo–parietal cortex; AP = arterial pressure.

TABLE II. *Effects of infusions of laudanosine 15.7 mg $kg^{-1}h^{-1}$ on mean arterial pressure and heart rate in three anaesthetized dogs (mean values ± SEM). Asterisks indicate significant differences from control (time 0 min): at the 5%*, 1%** and 0.1%*** levels, respectively*

Time (min)	Mean arterial pressure (mm Hg)	Heart rate (beat min^{-1})
0	126±3.8	173±6.7
5	125±6.2	170±5.8
10	122±6.0	167±13.3
15	104±26.2	147±12.0
20	115±26.4	167±20.3
25	79±17.4	127±3.3
30	63±6.1**	117±3.3*
45	54±1.7***	103±6.7*
60	57±3.5**	110±10.0*
75	57±6.5**	103±6.7*
90	56±5.8**	102±8.3*
120	56±5.4***	90±5.8*
150	56±4.3***	87±6.7**

TABLE III. *Mean plasma concentrations (± SEM where relevant) of laudanosine during infusion of 15.7 mg kg^{-1} h^{-1} to three dogs anaesthetized with halothane.** n = 2

Infusion time (min)	Laudanosine ($\mu g\ ml^{-1}$)
5	0.44±0.27
15	2.34±0.45
30	6.26±0.42
60	10.05±0.51
90	12.27*
120	14.76±1.01
150	17.16*
180	17.98*

Infusion studies in anaesthetized dogs

EEG recording. The infusion of laudanosine led to the progressive development of EEG seizure activity in all three dogs. This followed a similar pattern in each dog and the EEG changes reported below are illustrated with examples of recordings from a single dog (fig. 1A-F). Control EEG recordings from each animal showed a similar pattern, and were characterized by low amplitude and frequency. Fast activity, where present, was superimposed on slow waves. Sharp waves and spikes were generally absent (fig. 1A).

In all three animals, the infusion of laudanosine 15.7 mg kg^{-1} h^{-1} increased EEG frequency and amplitude 30±3.1 min after the start of the infusion (fig. 1B). After laudanosine had been infused for between 1.5 and 2 h, sharp waves and spikes were observed (fig. 1C) with an increase in rate between 2 and 3 h after the start of infusion to produce an EEG dominated by spiking, with polyspikes and paroxysmal bursts which gave rise to myclonic jerks, and facial twitches (fig. 1D). Despite the use of halothane anaesthesia each animal experienced a clonic seizure between 2.5–3.25 h after the start of the infusion of laudanosine. There was accompanying ictal EEG seizure activity (fig. 1E). In all animals seizure activity was arrested by the administration of diazepam 1–4 mg kg^{-1} i.v. (fig. 1F). Thus, in all three dogs, the infusion of laudanosine evoked the progressive development of EEG seizure activity culminating in clonic convulsions which were controlled by diazepam.

Cardiovascular changes. The constant infusion of laudanosine 15.7 mg kg^{-1} h^{-1} induced a significant decrease in arterial pressure after 30 min (63±2.9 mm Hg) (table II). Heart rate also decreased significantly (47±8.8 beat min^{-1}) (table II). The changes in arterial pressure and heart rate persisted for the duration of the study and are illustrated in figure 1A-F.

Laudanosine plasma concentrations. Mean plasma concentrations of laudanosine increased progressively during the infusion (table III; fig. 2).

Correlation of EEG seizure activity and plasma concentrations of laudanosine (fig. 2) indicated that the increases in EEG frequency and amplitude occurred with concentrations $> 6\ \mu g\ ml^{-1}$. Similarly, the appearance of EEG spiking occurred with plasma concentrations $> 10\ \mu g\ ml^{-1}$. Polyspikes, paroxysmal bursts and myoclonic activity were observed at laudanosine plasma concentrations $> 14\ \mu g\ ml^{-1}$, while clonic seizures occurred when plasma concentrations $> 17\ \mu g\ ml^{-1}$ were achieved.

Correlation of the changes in arterial pressure and heart rate and plasma concentrations of laudanosine indicated that significant decreases in arterial pressure and heart rate occurred at concentrations $> 6\ \mu g\ ml^{-1}$.

DISCUSSION

These studies in mice, rats and dogs have confirmed the previous observations of Babel (1899) and Mercier and Mercier (1955) that laudanosine induces convulsions in laboratory

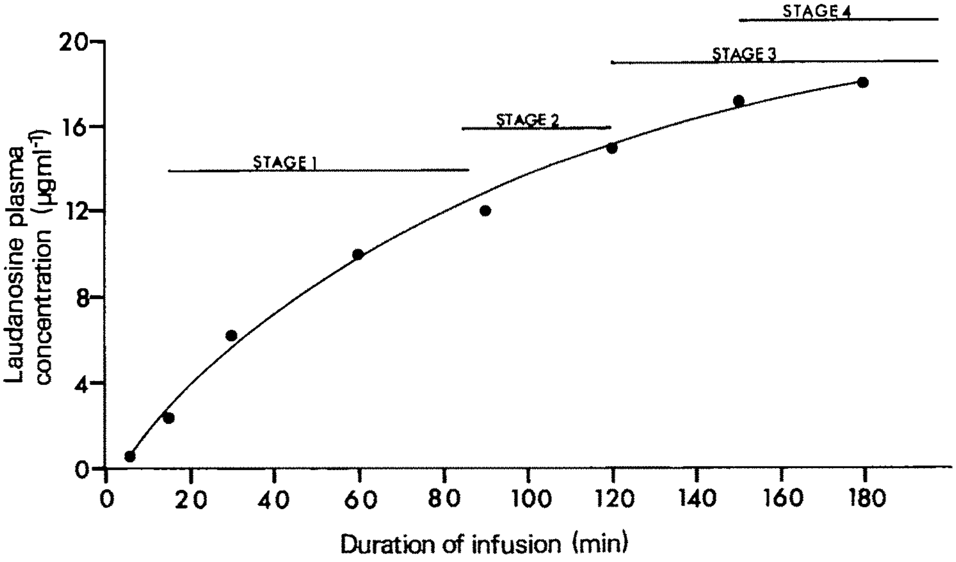

FIG. 2. Increase in mean plasma concentrations of laudanosine with time during constant i.v. infusion of 15.7 mg kg^{-1} h^{-1}, correlated with changes in the EEG of the anaesthetized dog. During Stage 1, EEG amplitude and frequency increased compared with control. Stage 2 marks the appearance of spiking and fast waves. Stage 3 EEG was dominated by spikes, polyspikes and paroxysmal bursts accompanied by myoclonus. During Stage 4, all three dogs experienced clonic convulsions.

animals. Such laudanosine-induced seizures may be prevented by pre-treatment with diazepam, but not by phenytoin, phenobarbitone, sodium valproate or ethosuximide. Although the dose of diazepam used in rats was high relative to clinical doses, it should be noted that diazepam and the other antiepileptic drugs were examined at single doses specifically chosen on the basis of results obtained using the maximal electroshock test. Diazepam is known to be less potent as an anticonvulsant in the maximal electroshock test compared with other standard anticonvulsant tests such as seizures induced by leptazol. It is also less potent as an anticonvulsant in rats. In the maximal electroshock test the drug has approximately one-third of the potency in the rat compared with the mouse (A. A. Miller and P. L. Wheatley, unpublished observation). Diazepam inhibited laudanosine-induced seizures in mice with an activity similar to that obtained in the maximal electroshock test (A. A. Miller and P. L. Wheatley unpublished observation).

In conscious dogs, laudanosine, administered by bolus injection or infusion, produced plasma concentrations insufficient to cause overt convulsions or other major behavioural disturbances. However, the plasma laudanosine concentrations (about 1.2 µg ml^{-1}) achieved in these animals were six times those observed after a bolus injection of atracurium 0.5 mg kg^{-1} i.v. in normal patients (Fahey et al., 1984).

In dogs anaesthetized with halothane, a constant rate infusion of laudanosine produced concentrations sufficient to evoke not only EEG seizure activity ($>$ 14 µg ml^{-1}), but frank behavioural convulsions ($>$ 17 µg ml^{-1}). Both effects were antagonized by diazepam. Previous control EEG recordings in dogs anaesthetized with 0.5–1% halothane for up 6 h have revealed no evidence of EEG seizures (P. Wheatley, unpublished observations). Indeed halothane anaesthesia has been found to increase the seizure threshold in rats, and has been shown to reduce greatly the severity of epileptic EEG spiking and behavioural convulsions induced by the infusion of leptazol (R. O'Donnell and P. Wheatley, unpublished observations). Therefore, it is possible that the laudanosine concentrations required to evoke seizures in this study were greater than those likely to be required in conscious animals because of the halothane anaesthesia.

Some comparisons are available between the plasma concentrations of laudanosine associated with convulsions in this study ($>$ 17 µg ml^{-1}) and those observed after atracurium administration in man. Studies in patients with normal renal function have demonstrated peak plasma concentrations of laudanosine of 0.199 ± 0.031 μg ml^{-1} 2 min after a bolus dose of atracurium 0.5 mg kg^{-1} (Fahey et al., 1984). Other studies in which bolus doses of atracurium 0.3–0.4 mg kg^{-1} were given i.v. to patients with normal and impaired renal function have demonstrated peak plasma laudanosine concentrations of 0.188 ± 0.022 and 0.267 ± 0.042 μg ml^{-1}, respectively, 2 min after administration (Ward et al., 1985). The results from these clinical studies, using bolus doses of atracurium, and the data from the anaesthetized dogs using laudanosine infusions, indicate a large difference between clinical plasma concentrations of laudanosine and those which may induce epileptiform EEG changes or induce convulsions after a single bolus dose of atracurium.

Laudanosine concentrations in plasma and CSF in dogs anaesthetized with halothane have been measured (Hennis et al., 1984): the CSF:plasma ratios were 0.3–0.6. Studies in man have given ratios ranging from 0.01 to 0.14 (Fahey et al., 1985). These laudanosine concentrations were measured after atracurium administration and not after laudanosine administration as in the previous study. It may be deduced from these results that either laudanosine crosses the blood–brain barrier less readily in man than in the dog, or man eliminates laudanosine from the CSF at a greater rate than does the dog. Either way, the implication is that there may be an even higher safety factor during the clinical use of atracurium.

Computer predictions by Ward and colleagues (1985), based on data from bolus administrations to anaesthetized patients, indicated that, after continuous infusions of atracurium 0.6 mg kg^{-1} h^{-1} for many days, plasma laudanosine concentrations could reach 1.0 ± 0.30 or 1.61 ± 0.31 μg ml^{-1}, in normal and renally impaired patients, respectively. In a study in the intensive care unit (Yate et al., 1985), infusions of atracurium 0.71–1.9 mg kg^{-1} h^{-1} for 40–139 h to sedated patients with normal and impaired renal function produced maximum plasma laudanosine concentrations within the range 1.9–5.1 μg ml^{-1}. The laudanosine concentrations in patients with impaired renal function were in the middle of the normal patient range. Although EEG monitoring was not performed, no convulsions were observed during regular patient assessment or during recovery.

The infusion rates used by Yate and colleagues (1985) were higher than those used by Ward and co-workers (1985) in their computer predictions. In some patients progressively greater rates of infusion were required to maintain neuromuscular blockade, probably as a result of an increase in extrajunctional acetylcholine receptors (P. M. Yate, personal communication). The concentrations of laudanosine obtained in the study by Yate and colleagues (1985) were just below those which correlated with increased EEG frequency and amplitude in dogs (fig. 2), but it should be noted that clonic seizure activity in dogs was not seen until plasma laudanosine concentrations > 17 μg ml^{-1} were produced (that is, approximately 3 to 7 times greater than those observed in the study by Yate and colleagues (1985)).

The excretion of laudanosine from the body after the administration of atracurium to anaesthetized cats has been shown to be 70% biliary and 30% urinary (Neill and Chapple, 1982). Clinical studies have confirmed that some laudanosine is excreted via the kidney (Ward et al., 1985). Other studies in the dog indicate that laudanosine can be metabolized, probably by the liver, to tetrahydropapaverine (D. J. Chapple and colleagues, unpublished observations). Higher plasma concentrations of laudanosine may, therefore, be anticipated in patients with poor hepatic or renal function.

In our studies in anaesthetized dogs, no cardiovascular effects were observed at plasma laudanosine concentrations up to 4 μg ml^{-1}. Significant decreases in heart rate and arterial pressure occurred with plasma laudanosine concentrations of 6 μg ml^{-1}. This is approximately 20 times the concentration of laudanosine measured after a full neuromuscular blocking dose of atracurium in patients. The cardiovascular effects differed in conscious dogs, in which increases in heart rate were observed. This may be the result of differences in dose and rates of infusions of laudanosine, but possibly may also reflect an interaction between halothane and laudanosine.

Hennis and colleagues (1984) have described signs of awakening after bolus dose of laudanosine 2 mg kg^{-1} i.v. in dogs anaesthetized with halothane. This was confirmed in rabbits where the MAC for halothane was increased by 30% when blood laudanosine concentrations were between 0.4 and 0.8 μg ml^{-1} (Miller, 1985). In our dog study, increases in the rate and depth of respiration were observed 19–24 min after the start of the laudanosine infusion (i.e. with plasma laudanosine concentrations of about 4 μg ml^{-1}).

These effects could be prevented or reversed by increasing the inspired halothane concentration from 0.5% to 1–2%. Respiratory changes of this magnitude or greater can be observed during normal surgery in the presence of neuromuscular blocking agents other than atracurium.

These studies have confirmed that laudanosine, a degradation product of atracurium, induces seizure activity in animals and have shown that the progressive convulsant action can be correlated with plasma concentrations in dogs. We conclude that the administration of atracurium to patients at the recommended doses, by bolus injection or short-term continuous infusion during surgery, is unlikely to result in concentrations of laudanosine capable of producing the seizure activity, or the cardiovascular changes that were observed in this animal study. However, caution should be exercised during the prolonged infusion of atracurium to patients, especially those with renal or hepatic failure, until more clinical experience has been obtained, although it is likely that laudanosine would be effectively removed from the circulation in these patients during routine haemodialysis. Such clinical experience has recently been reported by Wadon, Dogra and Anand (1986) and no evidence of drug related convulsive behaviour was observed.

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TUBOCURARINE AND PANCURONIUM INHIBIT EVOKED RELEASE OF ACETYLCHOLINE FROM THE MOUSE HEMIDIAPHRAGM PREPARATION

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SUMMARY

Using a sensitive radioactive method that measures selectively the evoked release of acetylcholine, it was demonstrated that, when stimulating at 50 Hz, tubocurarine or pancuronium 2×10^{-6} mol litre^{-1} or hexamethonium 10^{-3} mol litre^{-1} significantly decreased the evoked release of acetylcholine in the mouse in vitro *phrenic nerve–hemidiaphragm preparation.*

Liley and North (1953) demonstrated that, in the rat hemidiaphragm paralysed by tubocurarine, repetitive stimulation of the phrenic nerve caused a gradual decrease in the amplitude of the end-plate potential (EPP). They assumed that this was the result of a decreased release of transmitter, and that it was a physiological response to high frequency stimulation which was unmasked, but not produced, by tubocurarine (Otsuka, Endo and Nonomura, 1962). However, other workers (Hubbard, Llinas and Quastel, 1969; Blaber, 1970, 1973; Hubbard and Wilson, 1973; Bowman and Webb, 1976; Magleby, Pallotta and Terrar, 1981), using different methods, showed that the rate of attenuation of the EPP in high frequency trains was greater in the presence than in the absence of tubocurarine—a decrease attributed to the reduction of acetylcholine release (Hutter, 1952; Otsuka and Endo, 1960; Gibb and Marshall, 1984).

In agreement with the above findings, it has been reported that the neuromuscular blocking effects of tubocurarine and other non-depolarizing neuromuscular blocking drugs are greater during high frequency than during low frequency electrical stimulation *in vitro* (Foldes, Chaudhry et al., 1981) and *in vivo* both in animals (Paton and Zaimis, 1952; Bowman and Webb, 1976; Foldes, Chaudhry et al., 1981) and in man (Stanec and Baker, 1984). Bowman and Webb (1976) and Bowman (1980) suggested that the increase in the potency of non-depolarizing neuromuscular blockers at high rates of stimulation is, in part, the result of the inhibition of a positive, nicotinic feedback mechanism of acetylcholine release. According to Bowman (1980), the acetylcholine released by the nerve impulse acts, not only on the nicotinic (cholinergic) receptors of the postjunctional membrane, but also on nicotinic receptors of the motor nerve terminal. The interaction of acetylcholine with the latter results in an increase in the evoked release of acetylcholine. Because of the great safety margin of neuromuscular transmission (Paton and Waud, 1967), inhibition of this positive feedback mechanism only becomes important at relatively high (>2 Hz) rates of stimulation when the margin of safety is decreased to a level where any effect on the release of acetylcholine affects chemical neurotransmission (Foldes, Yun et al., 1981).

Until now, attempts to demonstrate the inhibitory effect of non-depolarizing neuromuscular blocking drugs on the evoked release of acetylcholine by neurochemical methods (assay of the

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released acetylcholine) have been unsuccessful. Various investigators reported that tubocurarine had little (Beani, Bianchi and Ledda, 1964) or no (Dale, Feldberg and Vogt, 1936; Emmelin and McIntosh, 1956; Straughan, 1960; Krnjevic and Mitchell, 1961; Cheymol, Bourilet and Ogura, 1962; Chang, Cheng and Chen, 1967; Fletcher and Forrester, 1975) effect on the evoked release of acetylcholine. In all of these studies the total (quantal + non-quantal) acetylcholine was measured in the presence of an anticholinesterase. The failure to demonstrate any changes in the evoked quantally released acetylcholine by tubocurarine may have been because most of the acetylcholine released from mammalian muscle and measured by bioassay is released in a non-quantal form. At rest, about 98 %, and during electrical stimulation about 70 %, of the released acetylcholine is non-quantal (Vizi and Vyskocil, 1979).

To resolve the contradiction between the results of the pharmacological and neurophysiological studies on the one hand and those of the direct measurement of acetylcholine on the other, the effect of non-depolarizing neuromuscular blockade on the evoked release of acetylcholine was re-examined with a sensitive radioactive method (Foldes et al., 1984). Radioactive choline was used to label the acetylcholine stores of the mouse hemidiaphragm preparation. It was shown previously that the newly synthetized ^{3}H-acetylcholine is preferentially released in response to electrical stimulation in brain (Szerb, 1975), myenteric plexus (Vizi et al., 1984), and also in the mouse hemidiaphragm preparation (E. S. Vizi, unpublished observations). Furthermore, using this method, measurement of acetylcholine release can be accomplished without cholinesterase inhibition (Szerb, 1975; Kilbinger and Wessler, 1980; Foldes et al., 1984; Vizi et al., 1984). This is advantageous because cholinesterase inhibitors are known to affect the release of acetylcholine (Fatt and Katz, 1952; Boyd and Martin, 1956; Foldes et al., 1984).

MATERIAL AND METHODS

Male Swiss–Webster mice of 25–30 g body weight were lightly anaesthetized with ether and decapitated. The middle portions of both hemidiaphragms (about 2–3 mm to the right and left of the insertions of the phrenic nerves), together with the attached rib segments, were suspended in organ baths of 2 ml volume in Krebs' solution (NaCl 113, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, $NaHCO_3$ 25, KH_2PO_4 1.2 and glucose 11.5 mmol litre^{-1}). The bath temperature was maintained at 37 °C. The pH of the solution aerated with a 95 % oxygen–5 % carbon dioxide gas mixture was 7.38–7.42. The rib end of the preparation was attached with a ligature to the bottom of the bath and its tendon to an FT03 transducer.

Stimulation. After 2 g resting tension was applied, the preparations were stimulated with a Grass S-88 stimulator by 0.8-s, 0.1-s or 1-s trains of 50-Hz, supramaximal impulses of 0.2 ms duration, every 10 s or 20 s through platinum electrodes placed above the proximal and below the distal parts of the preparation (field stimulation).

Peak tetanic tension. Tetanic fade. The isometric contractions were measured with force displacement transducers and continuously monitored on a polygraph recorder. The peak tetanic tension and tetanic fade were recorded as described by Bowman and Webb (1976).

Incubation. After a 15-min equilibration period, the preparations were loaded with ^{3}H-choline 5 μCi ml^{-1} for 60 min. The preparations were stimulated during this 75 min as described above. This was done to facilitate the incorporation of ^{3}H-choline into the acetylcholine pool of the motor nerve terminal. For the next 20 min, the preparations were allowed to rest. At the end of this period, in seven preparations the radioactivity of the muscles, consisting partly of ^{3}H-choline and partly of ^{3}H-acetylcholine, was $7.54 \pm 1.0 \times 10^5$ Bq g^{-1}. After being washed three times to remove excess ^{3}H-choline, each preparation was transferred to another bath and superfused with Krebs' solution at the rate of 2 ml min^{-1} for 60 min. From then on, throughout the investigations, Krebs' solution containing hemicholinium-3 5×10^{-5} mol litre^{-1} was superfused at a rate of 0.5 ml min^{-1}. Hemicholinium-3 was added to prevent reuptake of ^{3}H-choline that diffused out as such from the muscle or was liberated by hydrolysis of ^{3}H-acetylcholine released during the subsequent stimulation periods.

Collection. During superfusion at the rate of 0.5 ml min^{-1}, 3-min effluents were collected continuously with a fraction collector into scintillation vials throughout the rest of the experimental period. The preparations were stimulated, as described, three times for 3 min each starting at the 10th (S_1), 52nd (S_2) and 82nd (S_3) min.

In 14 control experiments, no drug was added to the perfusing solution. In six, eight and six other studies, respectively, tubocurarine 2×10^{-5} mol litre^{-1}, pancuronium 2×10^{-5} mol litre^{-1} or hexamethonium 10^{-3} mol litre^{-1} was added to the perfusing Krebs'–hemicholinium-3 solution at 17 min.

Calculation. In the mouse phrenic nerve–hemidiaphragm preparation, similar to the situation in the myenteric plexus–longitudinal muscle preparation of the guineapig ileum (Szerb and Somogyi, 1973; Kilbinger and Wessler, 1980; Vizi et al., 1984), electrical stimulation increases only the release of ^{3}H-acetylcholine and the outflow of ^{3}H-choline remains unchanged (E. S. Vizi, unpublished observations). Consequently, the evoked release of ^{3}H-acetylcholine can be calculated from the difference between the expected spontaneous and the actually measured outflow of radioactivity caused by 3 min of electrical stimulation. Spontaneous release was assumed to follow first-order kinetics. It was determined by the "least square" fitting to an exponential curve method of the Bq g^{-1} concentrations of two 3-ml effluents collected before, and that of two others collected after, every period of stimulation. The expected spontaneous outflow was obtained by interpolation between the fitted points.

The radioactivity of the samples was measured in a Packard Scintillation Beta Spectrometer. There was considerable variation in the controls from one preparation to the other, in the amount of radioactivity released during the corresponding periods of stimulation. In contrast, the ratios of radioactivity measured during the first two consecutive stimulation periods, S_2/S_1, were constant. Results are presented as mean values ± SEM.

Statistical analysis. The statistical significance of the results was determined by one-way analysis of variance of the logarithmically transformed data, followed by Dunn's test. $P < 0.05$ was considered significant.

TABLE I. *Inhibition of the evoked release of radioactivity from mouse hemidiaphragm preparations, loaded with ^{3}H-choline, by tubocurarine, pancuronium or hexamethonium. The inhibition of the evoked release of radioactivity could be attributed to the inhibition of the release of ^{3}H-acetylcholine (for explanation see text). * Ratio of the evoked release of radioactivity during the second and first stimulation periods (mean ± SEM). Significant differences from control determined by one-way analysis of variance followed by Dunn's test*

Compound	*n*	S_2/S_1 Ratio*	*P*
Control	14	0.79 ± 0.02**	—
Tubocurarine 2×10^{-6} mol litre^{-1}	6	0.42 ± 0.08	<0.01
Pancuronium 2×10^{-5} litre^{-1}	8	0.51 ± 0.08	<0.01
Hexamethonium 10^{-3} mol litre^{-1}	6	0.51 ± 0.07	<0.01

Materials. The materials used were ^{3}H-methylcholine chloride (Amersham, 78 Ci mmol litre^{-1}, tetrodotoxin (Sigma), eserine sulphate (Sigma), tubocurarine (BDH), pancuronium (Organon) and hexamethonium (BDH).

RESULTS

Resting release

In six investigations, the release of radioactivity at rest remained relatively constant (1513 ± 154 Bq g^{-1} min^{-1}) throughout. Tetrodotoxin 5×10^{-7} mol litre^{-1}, pancuronium 2×10^{-5} mol litre^{-1} and hexamethonium 3×10^{-3} mol litre^{-1} had no effect on resting release.

Evoked release

When trains of 40 stimuli (50 Hz) were delivered every 10 s for 3 min (720 stimuli were applied), the release of radioactivity was significantly enhanced above spontaneous release by 2685 ± 180 Bq g^{-1} ($n = 8$). The output of radioactivity was very constant; the ratio between the amounts of radioactivity released by consecutive stimulation periods (S_2/S_1, S_3/S_2) did not differ significantly from each other: S_2/S_1 was 0.83 ± 0.09 and S_3/S_2 was 0.72 ± 0.08 ($n = 8$ and 8, $P > 0.05$). Tetrodotoxin 5×10^{-7} mol litre^{-1}, added to the bath 10 min before stimulation, completely inhibited the stimulation evoked release of radioactivity.

Table I shows the effect of different antinicotinic agents (hexamethonium, tubocurarine and pancuronium) on the release of radioactivity in response to stimulation. All these agents signifi-

TABLE II. *Effect of different antinicotinic agents on neuromuscular transmission of and ^{14}C-acetylcholine release from mouse hemidiaphragm preparation. * Phrenic nerve was stimulated and trains of 50 Hz (five shocks) were delivered in every 20 s. The contractions were recorded isometrically. † The release of radioactivity was measured (see Methods). Trains of 50 Hz (40 shocks) were applied in every 10 s. ‡ The contractures produced by trains of 50 Hz (100 shocks) were recorded and the effect of drugs in different concentrations was studied on the maintenance. IC_{25} is the concentration needed to produce 25% reduction of maintenance*

	Inhibition of		
	Postjunctional	Prejunctional	
	Peak tetanic tension* (IC_{50}) (μmol litre^{-1})	^{3}H-ACh release (threshold concn) (μmol litre^{-1})†	Tetanic fade‡ (IC_{25}) (μmol litre^{-1})
Tubocurarine	0.86 ± 0.01	0.5	0.28 ± 0.02
Pancuronium	0.42 ± 0.02	0.25	0.18 ± 0.03
Hexamethonium	2430 ± 200	50	260 ± 12

cantly reduced the stimulation-evoked release of radioactivity. The threshold concentrations were found to be 0.5 µmol litre^{-1} for tubocurarine, 0.25 µmol litre^{-1} for pancuronium and 50 µmol litre^{-1} for hexamethonium, respectively (table II). They produced a significant reduction of ^{3}H-acetylcholine release: the S_2/S_1 ratios were 0.601 ± 0.03, 0.621 ± 0.03 and 0.641 ± 0.02, respectively ($n = 3$ and 3, $P < 0.01$). These data indicate that the effects of the neuromuscular blockers are concentration-dependent. The IC_{50} values for the inhibition of the peak tetanic tension of the mouse phrenic nerve–hemidiaphragm preparation were 0.86 ± 0.01 µmol litre^{-1} for tubocurarine, 0.42 ± 0.02 µmol litre^{-1} for pancuronium and 2430 ± 200 µmol litre^{-1} for hexamethonium (table II).

DISCUSSION

The sensitive radioisotope method (Foldes et al., 1984) used in this study revealed the significant inhibitory effect of tubocurarine on the evoked release of acetylcholine that could not be demonstrated by other methods (Dale et al., 1936; Emmelin and McIntosh, 1956; Krnjevic and Mitchel, 1961; Chang, Cheng and Chen, 1967; Fletcher and Forrester, 1975). The data presented are in agreement with the results of the electrophysiological (Hubbard, Llinas and Quastel, 1969; Blaber, 1970, 1973; Bowman and Webb, 1972; Hubbard and Wilson, 1973) and pharmacological (Paton and Zaimis, 1952; Bowman, 1980) studies which indicated that tubocurarine inhibits evoked release of acetylcholine. Pharmacological evidence has been obtained (Bowman, 1980) that an extra facilitated release by a feedback mechanism occurs at high frequencies of nerve impulses. Both tubocurarine and hexamethonium (Paton and Zaimis, 1952) are known to inhibit the pharmacological effects of acetylcholine at nicotinic receptor sites of autonomic ganglia. Consequently, the inhibition of the evoked release of acetylcholine by these compounds supports the assumption of a positive nicotinic feedback mechanism of evoked acetylcholine release (Bowman, 1980). It would be incorrect, however, to attribute the tetanic fade solely to the inhibition of this positive feedback mechanism by non-depolarizing neuromuscular blockers. It is conceivable that, in much higher than the threshold concentrations in which they inhibit evoked release of acetylcholine, neuromuscular blocking drugs inhibit some other unknown mechanism of stimulated acetylcholine release. Inhibition of the refilling of the readily available acetylcholine stores of acetylcholine (Elmquist and Quastel, 1965) may be such a mechanism. However, the finding (table II) that the threshold concentrations of neuromuscular blockers required to decrease the evoked release of acetylcholine and tetanic fade were slightly less than those that inhibited peak tetanic tension and tetanic fade indicate that even a marginal decrease of acetylcholine release might affect the integrity of neuromuscular transmission at higher stimulation rates. Decrease of the evoked release of acetylcholine per stimulus (volley output of acetylcholine) during tetanic stimulation was observed in both neurophysiological (Liley and North, 1953) and neurochemical (Foldes et al.,

1978) studies. The prejunctional inhibition of evoked release of acetylcholine by neuromuscular blockers is also involved in the production of tetanic fade, train-of-four fade and tetanic reduction of EPP. Even a small reduction in the output may produce a devastating "fade" of mechanical responses, when a proportion of the postjunctional receptors is occluded. Hence, a neuromuscular blocking drug, by occluding some of the postjunctional receptors, will exaggerate the consequences of its own prejunctional action to diminish release.

There is considerable variation between the relative potencies of tubocurarine, pancuronium and hexamethonium at pre- and postjunctional receptor sites (table II). The IC_{50} values of tubocurarine (0.86 ± 0.01 μmol litre^{-1}) and hexamethonium (2430 ± 200 μmol litre^{-1}) in the mouse phenic nerve–hemidiaphragm preparation required for the inhibition of peak tetanic tension elicited by short trains of tetani (50 Hz, five shocks, every 20 s) were higher than those required to decrease evoked acetylcholine release or produce tetanic fade. These findings indicate that there are important differences between pre- and postjunctional nicotinic receptors. This assumption has been already made by Gibb and Marshall (1984). The order of relative selectivity at prejunctional site is hexamethonium > tubocurarine > pancuronium. This is in good agreement with the *in vivo* observation of Bowman and Webb (1976) who demonstrated in cats that pancuronium affected primarily the peak tetanic tension, tubocurarine affected both peak tetanic tension and tetanic maintenance, and hexamethonium influenced primarily tetanic maintenance.

Since all voluntary muscle movements in man and other mammals are elicited by short trains of tetani (Zierler, 1974), the presynaptic inhibition of the evoked release of acetylcholine may have considerable physiological and clinical significance. This assumption is supported by findings in laboratory animals and by clinical observations. Thus, for example, the blocking potency of non-depolarizing neuromuscular blocking drugs and aminoglycoside- or polypeptide-type antibiotics is much greater in *in vivo* and *in vitro* nerve–muscle preparations stimulated with short trains of 50-Hz tetani than in those stimulated with single impulses at 0.1 Hz (Foldes, Chaudhry et al., 1981). In anaesthetized patients recovering from the effects of non-depolarizing neuromuscular blockade, at the time when the twitch tension elicited by single impulses (at 0.1 Hz) had returned to or above 95% of control, the T4/T1 ratio was only 0.55 (Foldes, Yun et al., 1981). Similarly, tetanic fade was found to be more sensitive to non-depolarizing neuromuscular blockers than the single twitch (Stanec and Baker, 1984).

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MINIMUM VOLUME OF DISCARD FOR VALID BLOOD SAMPLING FROM INDWELLING ARTERIAL CANNULAE

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SUMMARY

The volume of discard for valid blood sampling from indwelling femoral (leader cath) and radial (Venflon) arterial cannulae (with internal volume of cannula plus connecting tubing of approximately 2 ml) was investigated by analysing sequential 2-ml aliquots of 10-ml samples. The aliquots were analysed for pH, carbon dioxide tension, oxygen tension, standard bicarbonate, haemoglobin concentration, haemoglobin oxygen saturation and potassium concentration. Analysis of variance showed that, for these variables and these catheters, a valid blood sample was obtained after discarding 4 ml, but not after only 2 ml. The haemoglobin concentration, as measured by a Corning oximeter, provided good warning of inadequate discard.

Indwelling arterial cannulae are used widely in the intensive care unit to permit pressure monitoring and blood sampling. The patency of the cannulae and connecting tubing is maintained by flushing with heparinized saline. Before taking samples for analysis, the heparinized saline in the catheter must be discarded to avoid dilution. Personal observation showed that, in the intensive care unit in the University Hospital of Wales, the volume of discard varied, between clinicians, from 3 to 10 ml. Palermo, Andrews and Ellison (1980) have studied this problem in relation to the assessment of coagulation; Dennis and colleagues (1985) have studied it in relation to the measurement of blood-gas tensions, but only for a catheter of unspecified internal volume.

In order to ascertain the minimum discard volume needed to obtain a representative arterial blood sample, some relevant biochemical indices were analysed in the first 10 ml of fluid taken from arterial catheters in five 2-ml increments.

PATIENTS AND METHODS

Five patients scheduled for cardiac surgery, who had indwelling radial and femoral arterial cannulae *in situ*, were studied in the perioperative period. Approval was obtained from the local ethical committee. The radial cannula (Venflon 2, Viggo products, 1452-2, 20-gauge, deadspace volume 0.15 ml) and the femoral cannula (leader cath, Vygon, 124.15, 18-gauge, 18 cm, volume 0.2 ml) were connected to three-way taps (Connecta, Viggo Products, 4614-4, volume 0.1 ml) via 200-cm connecting tubing (lectro-cath, Vygon, 1155.20, volume 1.85 ml). The total volume of both systems was close to 2.1 ml. The volumes were determined by weighing each component, and each complete system, dry and full of water.

In each patient, each system was sampled on three separate occasions. On each occasion the sample consisted of five successive aliquots, each drawn into a separate 2-ml polypropylene syringe (Monoject). The syringes were heparinized using 0.5 ml of sodium heparin, 1000 u ml^{-1}, which was then discarded leaving only that volume ($\sim$0.05 ml) which remained in the hub of the syringe. All samples were taken by the same person (M.C.) to ensure that the technique and rate of sampling (about 10 s for 2 ml) were consistent.

Each aliquot was analysed in duplicate using a Corning 178 blood-gas analyser and Corning oximeter M2500 (Ciba Corning Ltd, Halstead, Essex) for: pH, carbon dioxide tension ($P\text{CO}_2$),

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TABLE I. *Means and standard errors of the differences (SED) of various sets of blood measurements on 2-ml aliquots taken sequentially through arterial catheters with approximately 2 ml internal volume.* *P < 0.001 *with respect to aliquot 5*

	Aliquot					
Variable	1	2	3	4	5	SED
$P\mathrm{o}_2$ (kPa)	23.6	22.5	22.2	22.3	22.2	1.13
$S\mathrm{o}_2$ (%)	—	96.4	96.5	96.4	96.4	0.05
pH	7.39*	7.43	7.42	7.43	7.42	0.005
$P\mathrm{co}_2$ (kPa)	0.58*	5.25*	6.00	6.08	6.12	0.13
StB (mmol litre^{-1})	11.9*	26.6*	29.0	29.2	29.2	0.40
K^+ (mmol litre^{-1})	0.5*	3.5*	4.0	4.0	4.0	0.07
Hb (g dl^{-1})	—	9.7*	10.6	10.6	10.6	0.06

oxygen tension ($P\mathrm{o}_2$), standard bicarbonate (StB), haemoglobin concentration (Hb) and haemoglobin oxygen saturation ($S\mathrm{o}_2$). The order in which the specimens were analysed was randomized separately for the initial and duplicate analyses. The potassium concentration (K^+) was measured once on the remaining serum using a Beckman ISE electrolyte analyser E2 (Beckman, High Wycombe, Bucks). Blood analysis, on well-mixed samples, was started within 5 min of collection and concluded within 30 min, the samples being kept at room temperature.

Statistics

With analysis of each batch of aliquots spread over 20–25 min, there was generally some deterioration of the sample with time. This deterioration was estimated for each variable with a linear regression technique (see Appendix) and the estimate used to correct all measurements to what each would have been if it had been made at the time of the first analysis of each batch. An analysis of variance was performed on the corrected measurements. The structure of this analysis (see Appendix) distinguished (1) random variation between patients, between samples, between aliquots and between measurements, and (2) systematic differences between catheters and between aliquots, and any systematic catheter–aliquot interaction. The catheter–aliquot interaction will reveal any tendency for contamination to become insignificant after fewer aliquots with one catheter than with the other.

The analysis of variance was performed using the Genstat statistical package, version 4.03 (Numerical Algorithms Group Ltd) on a Honeywell mainframe computer running under Multics release 10.1.

RESULTS

With a slight exception in the case of $P\mathrm{co}_2$ (see Appendix) there was no significant difference between catheters ($P > 0.1$) and no significant catheter–aliquot interaction ($P > 0.1$). Accordingly, the results for each variable are summarized in table I in terms of the mean, for each aliquot, of both analyses of all samples for both catheters. The differences between means should be interpreted by reference to the standard errors of the differences between the pairs of means, which are given in the last column. The oximeter was unable to read the first aliquot, because the haemoglobin was below the measurement threshold (5 g dl^{-1}). For interest, the rate of deterioration of the samples with time is shown in table II.

DISCUSSION

It can be seen that the first aliquot was clearly anomalous for most variables and that the second was also significantly different from the remainder for $P\mathrm{co}_2$, StB, K^+, and Hb.

Although the $P\mathrm{o}_2$ results show no significant difference between the aliquots, it is clear that the

TABLE II. *Coefficients of the regression equation* $\hat{y} = a + bx$, *where* y = *rate of change of variable with time (rate per min) and* x = *mean value of the two analyses (d.f. = 148)*

Variable	*a*	*b*	SE(*b*)
pH	−0.0072	0.00091	0.00113
$P\mathrm{co}_2$ (kPa)	−0.00135	0.00109	0.00051
$P\mathrm{o}_2$ (kPa)	0.333	−0.0156	0.0011
StB (mmol litre^{-1})	0.0144	−0.00114	0.00134
$S\mathrm{o}_2$ (%)	−1.66	0.0172	0.0086
Hb (g dl^{-1})	−0.0076	0.00045	0.00096

pattern of results mirrored that of $P\text{CO}_2$, StB, and K^+. The explanation no doubt lies in the fact that, in this study, the $P\text{O}_2$ of the first aliquot was essentially that of a specimen of heparinized saline equilibrated with air at room temperature and measured at 37 °C, and that the $P\text{O}_2$ values in our patients happened to be similar. If the $P\text{O}_2$ of the blood were more removed from that of the saline, then no doubt there would be significant differences between aliquots.

It would appear that, for the present variables, and for both types and sites of cannula (with a total internal volume of approximately 2 ml), valid results are obtained for all measurements after a 4-ml discard but not after a 2-ml discard. This is in agreement with Palermo, Andrews and Ellison (1980) who recommended a discard volume of twice the internal volume, on the basis of coagulation measurements on blood samples drawn through catheters of 1.5 and 1.8 ml internal volume. A close study of their results suggests that a smaller discard volume might possibly be adequate. On the other hand Dennis and colleagues (1985), measuring blood-gas tensions and spun haematocrit, found that a 20-gauge, 3.2-cm radial arterial cannula, together with a 7-ft (2.1-m) connecting tube required a discard volume of 10 ml before sampling was satisfactory. They did not state the internal volume of their system, but recommended that each intensive care unit should make a similar study to determine the appropriate volume. This may well be sound advice, since it can be inferred from table I that, whatever the internal volume of a catheter system, the minimum discard volume will depend on (1) the extent to which the measurement is altered by the contaminating flushing fluid and (2) the extent of the error in measurement that is acceptable. In addition, it is conceivable that the speed at which the sample is drawn may affect mixing in the catheter and, hence, may influence the result.

With most of the variables in this study, the true value in a patient can change rapidly, often without clinical signs. Therefore, if the measurement of one of these variables changes from one blood sample to the next, it may be impossible, from that measurement alone, to discriminate between a true change and contamination of the sample. However, major changes in haemoglobin concentration are associated with marked clinical signs and symptoms (e.g. acute blood loss) or with clinical intervention (e.g. fluid administration). Accordingly, an unexpectedly low haemoglobin concentration can be an indicator of inadequate discard volume. Therefore, the concurrent, routine determination of haemoglobin concentration in all blood samples for blood-gas and potassium analysis could help identify invalid samples.

Invalidity of the sample is of particular importance in the case of potassium concentration. If this is falsely reported to be low, it is likely that potassium will be administered and this can result in cardiac arrhythmia and even arrest.

CONCLUSION

With the widespread use of indwelling arterial cannulae for blood sampling, the importance of reliable samples is paramount and the removal of an adequate discard volume before sampling is mandatory. In the catheters used in our intensive care unit, with a deadspace of approximately 2 ml, and for the variables measured in this paper, a discard volume of 4 ml is adequate.

It is tempting to assume that discarding a volume of twice the deadspace will always be adequate but, until this is established for several different circumstances, it would be prudent to verify the performance in any particular circumstance. If the interest is solely in concentrations, it should be adequate to measure just one substance which is present in blood and absent from the flushing liquid. Other properties of blood might conceivably be influenced by trace contamination by flushing liquid, although this did not appear to be the case with the coagulation measurements of Palermo, Andrews and Ellison (1980).

Oximeter measurement of haemoglobin concentration can give warning of inadequate discard.

APPENDIX

CORRECTION FOR DETERIORATION OF SAMPLE WITH TIME

The rate of change with time of each variable (except for K^+, which was measured only once per aliquot) was estimated for each aliquot according to $\dot{y} = (r_2 - r_1)/(t_2 - t_1)$ where t_1 and t_2 are the times and r_1 and r_2 are the results of the two analyses. The rate of change of a variable may vary with its actual value: for example, a low $P\text{O}_2$ will tend to increase towards the $P\text{O}_2$ of air; a high $P\text{O}_2$ will tend to decrease. Therefore, the linear regression equation $\dot{y} = a + bx$, where x is the mean of r_1 and r_2, was fitted to the values of y calculated as above for each variable. The resulting values of a and b are given in table II, together with the standard errors of b. From these it follows that the coefficients b (dependence of rate of change with time

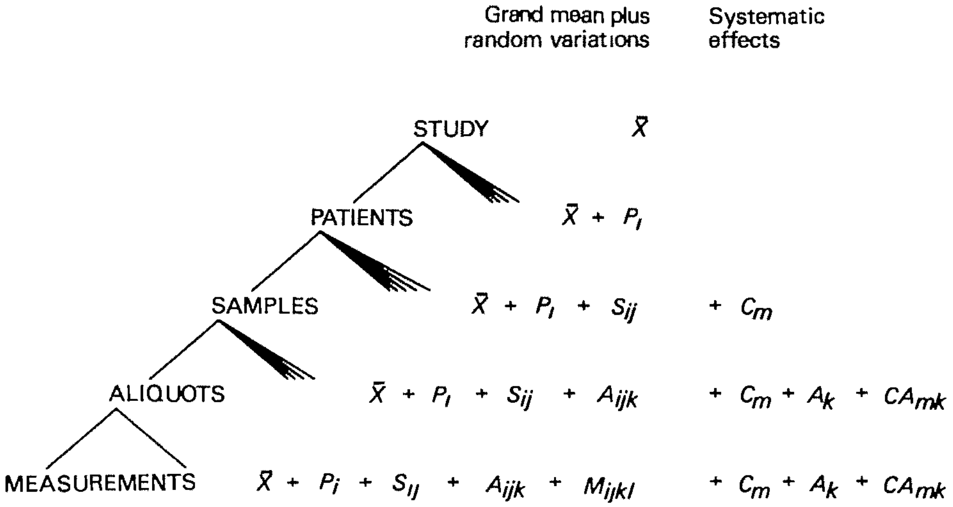

FIG. 1. Diagram of the structure of the analysis of variance of the results.

on mean value) vary from very highly significant for $P\text{o}_2$ (Student's $t = 14$) to non-significant for some other variables. It is also interesting to note that the values of a and b for $P\text{o}_2$ indicate that the rate of change of $P\text{o}_2$ would be zero at $0.333/0.0156 = 21.3$ kPa, that is, close to the partial pressure of oxygen in the atmosphere.

For consistency, all readings of all variables were corrected to what they were estimated to be at the time of the first analysis of each sample according to: corrected reading $= r-(a+bx)\times t$, where t is the time since the first analysis of a sample.

ANALYSIS OF VARIANCE

The analysis-of-variance model used is shown diagrammatically in figure 1. Each individual (corrected) reading is the sum of:

(1) The grand mean of all readings: $\bar{X}$

(2) The following random (error) variations:

Patient stratum: P_i = deviation of mean of all measurements on ith patient ($i = 1$ to 5) from grand mean.

Sample stratum: S_{ij} = deviation of mean of all measurements on jth sample ($j = 1$ to 6) (from ith patient) from mean for ith patient (corrected for the systematic effect of the relevant, mth, catheter—see below).

Aliquot stratum: A_{ijk} = deviation of mean of all measurements on kth aliquot ($k = 1$ to 5) (of jth sample from ith patient) from mean for jth sample from ith patient (corrected for the systematic effect of the kth aliquot and for the systematic interaction effect between the mth catheter and the kth aliquot—see below).

TABLE III. *Mean values of* $P\text{co}_2$ *(kPa) for each aliquot from each catheter*

	Aliquot				
Catheter	1	2	3	4	5
Femoral	0.59	5.55	6.32	6.40	6.48
Radial	0.57	4.98	5.71	5.78	5.78
Difference	0.02	0.57	0.61	0.62	0.70

Measurement stratum: M_{ijkl} = deviation of lth measurement ($l = 1$ or 2) (of kth aliquot of jth sample from ith patient) from mean for kth aliquot of jth sample from ith patient.

(3) The following systematic ("treatment") variations:

Catheter effect: C_m = deviation of mean of all measurements from mth catheter ($m = 1$ or 2) from grand mean.

Aliquot effect: A_k = deviation of mean of all measurements on kth aliquot from grand mean.

Catheter–aliquot interaction: CA_{mk} = deviation of mean of all measurements on kth aliquot from mth catheter from (grand mean $+ C_m + A_k$).

Plotting residuals against fitted values showed that the former were reasonably normally distributed although, with $P\text{co}_2$, StB and K$^+$, the variance of the residuals was somewhat different for the first aliquot from that for the remainder. However, when the analysis of variance was repeated for these three variables with only the last four aliquots included, the second aliquot was still highly significantly different from the fifth.

RESULTS FOR $P\text{co}_2$

$P\text{co}_2$ was the only variable with any suggestion of a difference between catheters (variance ratio 5.0; d.f. 1, 24; $0.025 < P < 0.05$) or catheter–aliquot interaction (variance ratio 2.2; d.f. 4, 112; $0.05 < P < 0.1$). However, table III shows that the difference between catheters was almost the same for all the last four aliquots. The simplest explanation of this is that the true mean $P\text{co}_2$ of the 15 samples drawn through the femoral catheter happened, by chance, to be about 0.6 kPa greater than that of the 15 drawn through the radial catheter.

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IN VIVO RELEASE OF CYANIDE FROM SODIUM NITROPRUSSIDE

J. C. NORRIS AND A. S. HUME

SUMMARY

Brain cytochrome oxidase activity was measured after the in vitro *addition of potassium cyanide (KCN) or sodium nitroprusside (SNP). Activity of cytochrome oxidase was sensitive to KCN; however, this activity was unaffected by SNP. In SNP- and KCN-treated animals brain cytochrome oxidase activities were measured. At 3 min after SNP injection, inhibition of the enzymatic activity was the same as 1 min after KCN injection. Time to death for SNP-treated animals was longer than for KCN-treated animals. These data suggest that cyanide was released* in vivo *from SNP and that time was necessary for this release to occur.*

The administration of sodium nitroprusside (SNP) ($Na_2[Fe(CN)_5NO]$) has been associated with a number of fatalities (Jack, 1974; Merrifield and Blundell, 1974; Davies et al., 1975). Previously, the mechanism behind these deaths had been ascribed to the five cyanide groups which comprise SNP—several reports having demonstrated that the cyanide moieties were released in blood (Vesey et al., 1974; Davies et al., 1975; Smith et al., 1977). However, Bisset and colleagues (1981) reappraised the release of cyanide from SNP and concluded that the cyanide found in the blood of SNP-treated patients was artefactual. These researchers proposed that exposure to light resulted in the conversion of the nitroprusside ion to aquapentacyanoferrate ion. This latter ion was considered to be unstable under the low pH used to analyse for cyanide and, thus, cyanide was released as the aquapentacyanoferrate ion decomposed.

This paper precipitated correspondence which rejected their explanation (Vesey, Cole and Simpson, 1982; Smith, Kruszyna and Kruszyna, 1982); the writers emphasized that there was ample evidence to support the *in vivo* release of cyanide from SNP. Graham and Rigg (1983) tested infusions of SNP for cyanide and found "no significant amounts of cyanide". Bisset, Butler and Glidewell (1984) responded that Graham and Rigg had used an equilibrium condition with a low pH and, consequently, they would not expect to detect any artefactual release of cyanide with this method of analysis. Unfortunately, Graham and Rigg (1983) did not continue the study by analysing for cyanide in blood samples from patients who had received SNP.

The object of this present work was to determine whether cyanide is released from the nitroprusside ion *in vivo*. Brain cytochrome oxidase activity was used as the method for the detection of the presence of cyanide in order to circumvent the problems associated with the earlier studies.

MATERIALS AND METHODS

Male ICR mice (from Charles River Laboratory, Inc., Wilmington, MA) weighing 25–30 g were used. Mice had access to food and water *ad libitum* and were housed in a temperature- and light-controlled environment.

Cytochrome c (95–100%; horse heart; Type VI) and sodium nitroprusside (SNP) were obtained from Sigma Chemical Company (St Louis, MO). Potassium cyanide (KCN) was purchased from Aldrich Corporation (Milwaukee, WI). Potassium ferricyanide was procured from Mallinckrodt Chemical Works (Belgium). Sodium mono- and di-basic phosphate were obtained from J. T. Baker Chemical Company (Phillipsburg, N.J.). Reagent grade chemicals were used through-

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out these studies. Solutions of SNP and KCN were made just before use in physiological saline (0.9% sodium chloride). Solutions of SNP were kept in a dark environment and removed only for long enough for injection to the animals. All injections were administered i.p.

Measurement of brain cytochrome oxidase activity was made by the method of Isom, Burrows and Way (1982). The brain was removed from the decapitated mouse and within 30 s homogenization had begun. Each brain was homogenized in a Potter–Elvejhem homogenizer with a motorized Teflon pestle in 2 ml of sodium phosphate 0.03 mol litre^{-1} buffer (pH 7.4) at 4 °C. This homogenate was diluted 1:40. These homogenates were maintained in an ice bath at 4 °C. Twenty microlitre of the diluted homogenate was mixed with the cytochrome c solution. The enzymatic activity was monitored as a decrease in the absorbance of this mixture at 550 nm with a Cary 17 spectrophotometer. Cytochrome c was completely oxidized by the addition of potassium ferricyanide. The difference in absorbance between completely reduced and oxidized cytochrome c was used to calculate enzymatic activity which was expressed as cytochrome c oxidized (μmol min^{-1}/mg protein). Protein concentrations were measured as described by Lowry and co-workers (1941). Brains from naïve animals were used in the *in vitro* studies.

Duncan's multiple range test was used to determine statistical difference between groups.

Ten to 20 animals received various doses of SNP or KCN to determine the lethality induced by SNP or KCN. From these data, the doses of SNP and KCN were selected which would induce 80% lethality. These doses were approximately 15 mg kg^{-1} i.p. for SNP and 8 mg kg^{-1} i.p. for KCN. This dose was then administered to animals used in (1) brain cytochrome oxidase activity studies and (2) the time of death study. Ten animals were given the SNP or KCN dose in the time of death study. Student's t test was used to determine statistical difference between the time of death for animals given SNP or KCN.

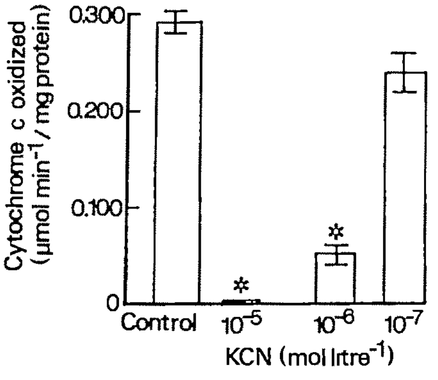

FIG. 1. Brain cytochrome oxidase activity after the *in vitro* addition of potassium cyanide (KCN). Asterisks indicate a statistical difference from control values ($P < 0.05$). The bars represent mean ± SEM of $n = 4$.

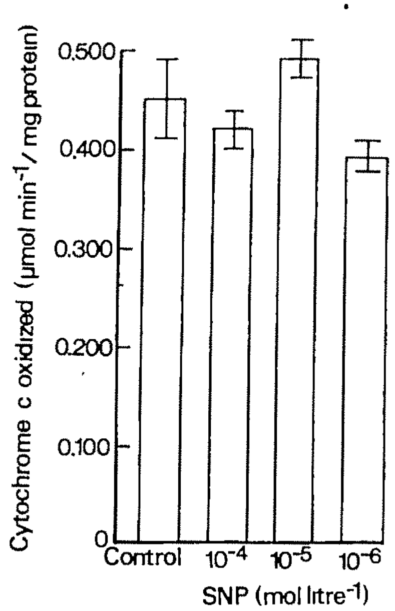

FIG. 2. Brain cytochrome oxidase activity after the *in vitro* addition of sodium nitroprusside (SNP). The bars represent mean ± SEM of $n = 4$.

RESULTS

In vitro inhibition of brain cytochrome oxidase (BCytox) activity by potassium cyanide (KCN) was performed to establish the sensitivity of the assay to the presence of cyanide. The results are illustrated in figure 1. These data show that there was complete inhibition of BCytox activity with KCN 10^{-5} mol litre^{-1}, 83% inhibition with KCN 10^{-6} mol litre^{-1} and no inhibition with KCN 10^{-7} mol litre^{-1}.

The effect of sodium nitroprusside (SNP) on BCytox activity was determined (fig. 2). These data demonstrate that the *in vitro* addition of SNP resulted in no inhibition of BCytox activity in the concentration range of 10^{-4}–10^{-6} mol litre^{-1}.

In vivo inhibition of BCytox activity after administration of an LD_{80} dose of KCN is

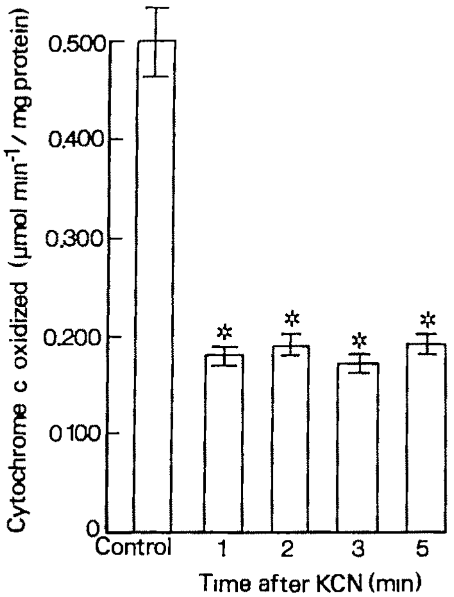

FIG. 3. Effect of an LD$_{80}$ dose of potassium cyanide (KCN) on brain cytochrome oxidase activity. Asterisks indicate a statistical difference from control values ($P < 0.05$). The bars represent mean ± SEM of $n = 4$.

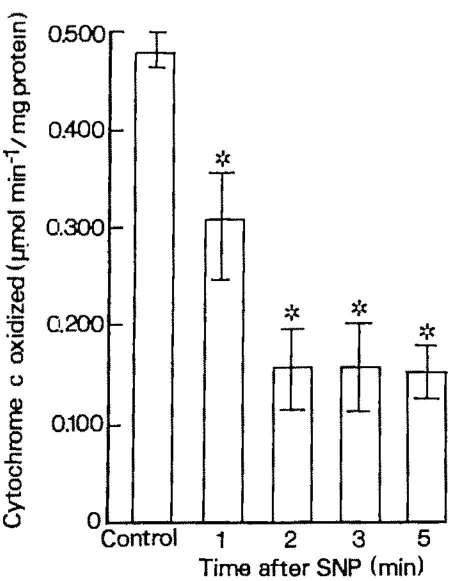

FIG. 4. Effect of an LD$_{80}$ dose of sodium nitroprusside (SNP) on brain cytochrome oxidase activity. Asterisks indicate a statistical difference from control values ($P < 0.05$). There was no statistical difference between cytochrome oxidase activities of SNP-treated animals. The bars represent mean ± SEM of $n = 4$.

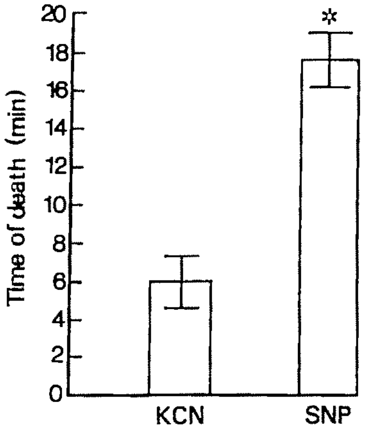

FIG. 5. Time interval between administration of an LD$_{80}$ dose of potassium cyanide (KCN) or sodium nitroprusside (SNP) and death. The asterisk indicates a statistical difference between KCN- and SNP-treated animals ($P < 0.05$). The bars represent mean ± SEM of $n = 10$.

illustrated in figure 3. This time course of enzymatic inhibition shows that, 1 min after the injection of KCN, there was a 60% inhibition of BCytox activity. The inhibition remained at that value at the other times at which BCytox activity was measured.

Data for the time course of the inhibition of BCytox activity in animals administered an LD$_{80}$ dose of SNP are illustrated in figure 4. One minute after the SNP injection there was inhibition of BCytox activity; however, it was only 37% of control activity. At 2-min, the inhibition was 49% of control activity. It was not until 3 min that the enzymatic inhibition was 60% of control activity.

An LD$_{80}$ dose of KCN or SNP was administered to animals, and the time interval between the injection and death was measured. Figure 5 demonstrates these data and shows that KCN-treated animals died 5.90 ± 1.28 min after the injection, while SNP-treated animals died 17.52 ± 1.38 min after the injection.

DISCUSSION

The controversy concerning the release of cyanide from sodium nitroprusside (SNP) has been mainly the result of the methods of analyses. Consequently, these data were collected using criteria which would avoid those conditions artefactually promoting the conversion of nitroprusside ions to aquapentacyanoferrate ions and their degradation to cyanide ions. These criteria were: (1) SNP solutions were made fresh and maintained in a dark and cool environment; (2) studies were conducted without the use of clinical apparatus (infusion tubing, reservoir solutions and drip chambers) so as to eliminate unnecessary exposure to light; and (3) biochemical analyses for cyanide were measured by cytochrome oxidase activity in whole brain. This assay was chosen because cyanide is known to inhibit cytochrome oxidase (Keilin, 1929), making this assay an excellent indicator of the presence of cyanide. Also, it required no extreme pH (7.4) and had a short time of assay (approximately 3 min) which circumvents criticism of previous analyses. In order to verify the significance of any inhibition of brain cytochrome oxidase (BCytox) activity after the administration of SNP, parallel studies were performed with an equally lethal dose of potassium cyanide (KCN).

Validation of this biochemical assay was accomplished in two steps. First, the sensitivity of BCytox activity to the presence of cyanide was determined and found to be acceptable: KCN 10^{-6} mol litre^{-1} inhibited 83% of control activity. Second, BCytox activity was found to be unaffected by the *in vitro* addition of SNP. The design of the study would have promoted these results. For example, the time of exposure to light used was much shorter than the time reported to induce any substantial conversion of SNP to aquapentacyanoferrate ions (Vesey, Cole and Simpson, 1976; Vesey and Batistoni, 1977; Arnold, Longnecker and Epstein, 1984). Thus the probability of the presence of any significant number of aquapentacyanoferrate ions would be negligible. However, if there were any aquapentacyanoferrate ions present, the release of cyanide would be abated since this release is reported to occur in an extropy process (Butler, Glidewell and Bisset, 1982). Since all samples were maintained at 4 °C except for the 3 min assay time, the design would retard any artefactual cyanide release from aquapentacyanoferrate ions. Thus, any inhibition of BCytox activity from SNP-treated animals could be adequately substantiated as the result of the release of cyanide *in vivo*.

The administration of SNP or KCN did produce inhibition of BCytox activity. In KCN-treated animals, BCytox activity was inhibited by 60% 1 min after injection, whereas, in the SNP-treated animals 60% inhibition of BCytox activity did not occur until 3 min after the injection. The inhibition of BCytox activity in SNP-treated animals suggests not only that cyanide was released from SNP *in vivo*, but also that there was a time interval necessary for this release to occur. This time interval could also explain the longer time to death in the SNP-treated animals compared with the KCN-treated animals.

These data provide evidence that cyanide was, indeed, released from SNP *in vivo*. Consequently, caution should be exercised when SNP is administered in a clinical setting.

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ESTIMATION OF ARTERIAL $P\mathrm{CO}_2$ DURING HIGH FREQUENCY JET VENTILATION

Studies in the Dog

A. J. MORTIMER, D. P. CANNON AND M. K. SYKES

SUMMARY

The arterial to end-tidal $P\mathrm{CO}_2$ *difference* ($Pa_{\mathrm{CO}_2} - P\mathrm{E}'_{\mathrm{CO}_2}$) *was measured in five anaesthetized dogs during controlled ventilation at 0.25 Hz (15 b.p.m.) and during high frequency jet ventilation at 1, 3 and 5 Hz. Because of the slow response of the infra-red carbon dioxide analyser, satisfactory recordings of end-tidal carbon dioxide could not be obtained at frequencies greater than 1 Hz. The interruption of high frequency jet ventilation by conventional ventilation resulted in approximately equal arterial and end-tidal* $P\mathrm{CO}_2$ *values during the first breath, and restoration of the normal arterial to end-tidal* $P\mathrm{CO}_2$ *difference by the third breath. It is concluded that, when high frequency jet ventilation at 1, 3 or 5 Hz is interrupted with normal tidal volumes at low frequencies, the arterial* $P\mathrm{CO}_2$ *can be estimated from recordings of the end-tidal* $P\mathrm{CO}_2$.

When healthy patients are anaesthetized and ventilated with normal tidal volumes at low frequencies, the arterial $P\mathrm{CO}_2$ (Pa_{CO_2}) may be estimated from the end-tidal $P\mathrm{CO}_2$ ($P\mathrm{E}'_{\mathrm{CO}_2}$) by assuming an arterial to end-tidal $P\mathrm{CO}_2$ difference ($Pa_{\mathrm{CO}_2} - P\mathrm{E}'_{\mathrm{CO}_2}$) of 0.8–1.0 kPa (Nunn and Hill, 1960). However, during high frequency jet ventilation (HFJV), when small tidal volumes are delivered at frequencies between 1 and 10 Hz, ($Pa_{\mathrm{CO}_2} - P\mathrm{E}'_{\mathrm{CO}_2}$) appears to increase as the frequency of ventilation increases (Capan et al., 1981; Rolly and Versichelen, 1983), so that the estimation of Pa_{CO_2} becomes inaccurate.

Whitwam and colleagues (1983), have shown that the normal ($Pa_{\mathrm{CO}_2} - P\mathrm{E}'_{\mathrm{CO}_2}$) can be restored by the application of several large breaths during a brief interruption of HFJV at frequencies up to 1.7 Hz. The purpose of the present study was to determine whether the technique could be extended to frequencies up to 5 Hz, and to examine the restoration of the normal ($Pa_{\mathrm{CO}_2} - P\mathrm{E}'_{\mathrm{CO}_2}$) in more detail.

MATERIALS AND METHODS

Five dogs of different breeds, weighing between 16 and 27 kg, were studied. After premedication with morphine 2–3 mg kg^{-1}, anaesthesia was induced with thiopentone 30 mg kg^{-1} i.v. and pentobarbitone 2–3 mg kg^{-1} i.v., and then maintained with a continuous infusion of pentobarbitone 1–2 mg kg^{-1} h^{-1}. The trachea was intubated with a tracheal tube which had two narrow-bore tubes incorporated to its wall (Hi-Lo jet ventilation tube, Mallinkrodt, U.K.). The two small-bore tubes were used to monitor airway pressure and carbon dioxide concentration while the lungs were ventilated through the large lumen (9 mm i.d.) which was connected directly to the inflation valve of a Nuffield 200 ventilator (Penlon, U.K.).

During the periods of HFJV, the Nuffield 200 ventilator was replaced with a time-cycled solenoid-operated jet ventilator, driven by 100% oxygen supplied at 400 kPa. The pulses of oxygen from the ventilator were delivered to the centre of the lumen of the tracheal tube, through a 1.8-mm i.d. nozzle fixed into a T-piece connector (Bourgain, Mortimer and Sykes, 1986). To ensure

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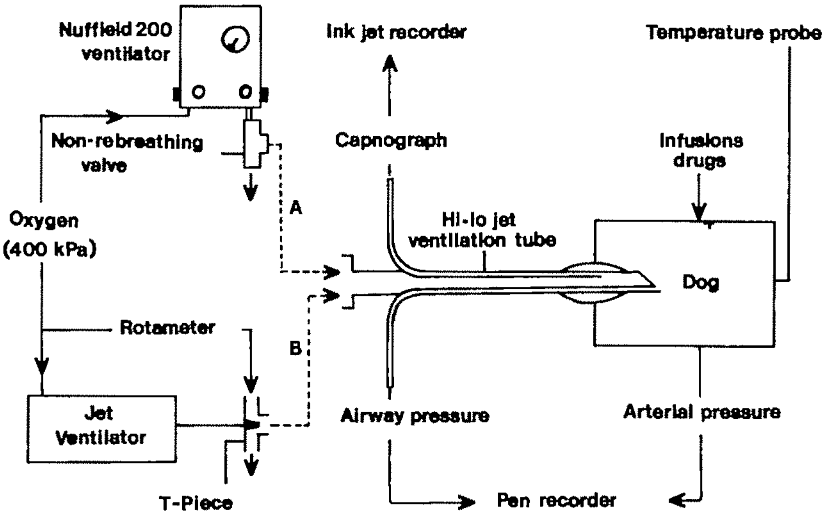

FIG. 1. Arrangement of study: the lungs are ventilated to normocapnia through the Hi-Lo jet ventilation tube either at 0.25 Hz with the Nuffield 200 ventilator (A) or at 1, 3 or 5 Hz with the high frequency jet ventilator (B). When conditions are stable using system B, the jet ventilator is rapidly disconnected from the tracheal tube and replaced immediately with system A. The changes in airway P_{CO_2} are recorded during the first eight breaths following the change of ventilator.

that no carbon dioxide was entrained when the frequency was 1 Hz (Mortimer and Bourgain, 1983) a 15 litre min^{-1} flow of oxygen was directed across the T-piece.

The carbon dioxide concentration was measured with an infra-red analyser (Gould Mark III), calibrated with oxygen and 10% carbon dioxide in oxygen, and the output displayed on a high frequency response ink-jet recorder (Siemens–Elema Mingograph). Gas was sampled at 180 ml min^{-1} through silicone tubing 30 cm long and 2 mm i.d., connected directly to the inlet on the front panel of the instrument, thereby bypassing the water trap.

A femoral arterial catheter was used to permit monitoring of arterial pressure and to allow intermittent blood sampling. Arterial blood-gas analyses were performed with an automated blood-gas analyser (Radiometer ABL2, Denmark), the measurements being corrected to the temperature of the dog (38 °C), which was monitored with a rectal thermistor and maintained at 38 ± 0.5 °C by a heated table. Drugs and fluids were administered through a catheter placed in a femoral vein. The airway and arterial pressures were measured with Druck PDCR75 transducers and displayed on a heated stylus recorder (Lectromed M19, U.K.).

The preparation of each animal included the surgical removal of the upper and cardiac lobes of the left lung because the animals were also used for a separate study on the distribution of pulmonary blood flow. Blood loss during the surgical preparation was replaced with a colloid solution (Haemaccel Polygeline, Hoechst, U.K.); fluid balance during the investigation was maintained with 4% dextrose in 0.18% saline. Non-respiratory acidosis was corrected with an infusion of 8.4% sodium bicarbonate to maintain the base excess within ± 1 mmol $litre^{-1}$. The arrangement of the equipment is shown in figure 1.

Plan of investigation

First investigation. Initially, the Pa_{CO_2} was adjusted to 5.0 ± 0.2 (SD) kPa by altering the tidal volume using the inspiratory flow control of the Nuffield 200 ventilator, the inspiratory: expiratory (I:E) time ratio being 1:2 and the frequency 0.25 Hz. After conditions had stabilized, a control arterial blood sample was obtained and the end-tidal and minimal airway carbon dioxide concentrations recorded. High frequency jet ventilation was then applied, using an I:E ratio of 1:2 and a frequency of 1, 3 or 5 Hz, the tidal volume being adjusted to produce a Pa_{CO_2} similar to control conditions by varying the regulator governing the oxygen driving pressure. When

TABLE I. *Arterial, end-tidal and minimal airway* $P\text{CO}_2$ *partial pressures (kPa) at four frequencies of ventilation (control = 0.25 Hz) (mean ± SD)*

Frequency (Hz)	n	$P\text{CO}_2$ (kPa) Arterial	End-tidal	Minimal
0.25	15	4.97±0.14	3.99±0.21	0.00±0.00
1	12	4.93±0.14	3.97±0.14	0.09±0.09
3	12	4.98±0.14	1.23±0.42	0.39±0.14
5	12	4.96±0.12	0.86±0.35	0.53±0.25

repeated blood-gas measurements indicated that conditions had been stable for 15–20 min, the measurements of blood and airway $P\text{CO}_2$ were repeated. The T-piece was then rapidly disconnected from the tracheal tube and the Nuffield 200 ventilator reconnected without changing the previous settings, the airway carbon dioxide concentration being recorded continuously during the first eight breaths after the change of ventilator. High frequency jet ventilation was recommenced at a different frequency and another set of measurements obtained after 15–20 min. The inspired gas was 100% oxygen during all measurements and the three high frequencies were applied in random order, with two or more measurements at each frequency being obtained in each animal.

All the measurements of carbon dioxide concentration were recorded at ambient temperature and pressure saturated (ATPS). To compensate for the presence of water vapour in alveolar gas, each reading was corrected to body temperature and pressure saturated (BTPS) at 38 °C. The data have been compared by analysis of variance and paired *t* tests where indicated. The significance level used was $P < 0.05$.

Second investigation. Since ($Pa_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}$) may be influenced by the response characteristics of the capnograph and recorder (Jones, Robertson and Kane, 1979), a second study was carried out to define these—the capnograph and recorder being used in a manner similar to that in the animal study. The system described by Schena, Thompson and Crone (1984) was used for this purpose. A cylinder containing 5% carbon dioxide in oxygen was connected via a pressure regulator to a solenoid valve and the tip of the sampling tube from the carbon dioxide analyser placed in the outlet of the valve. Simultaneous recordings of the electrical signals supplied to the solenoid valve, and the capnograph response to a single step increase in carbon dioxide concentration from 0 to 5%, were obtained. Measurements were also made under pulsatile conditions cycling the solenoid valve at 1, 3 and 5 Hz, with an on-time of 55% of each cycle.

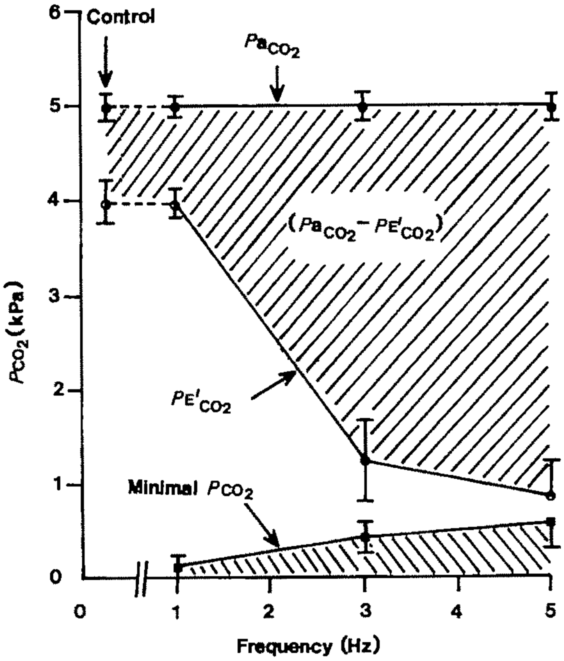

FIG. 2. Relationship between minimal airway and end-tidal $P\text{CO}_2$ with increasing frequency of ventilation at constant arterial $P\text{CO}_2$. Results are mean ± SD ($n = 12$ for each group apart from the control group, in which $n = 15$).

RESULTS

First investigation

There were no significant differences between Pa_{CO_2} values at each of the frequencies of ventilation studied (table I), the mean value ($n = 51$) being 4.96±0.13 (SD) kPa. During the control period of ventilation at 0.25 Hz, there was a significant difference ($P < 0.001$) of 0.98 kPa between the Pa_{CO_2} and $P\text{E}'_{\text{CO}_2}$. The arterial to end-tidal $P\text{CO}_2$ difference was similar in magnitude at 1 Hz, but at 3 Hz and 5 Hz, ($Pa_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}$) increased (fig. 2). The minimal airway $P\text{CO}_2$ was zero under control conditions, was just above zero at 1 Hz and increased progressively with frequency up to 5 Hz (table I, fig. 2).

The values of $P\text{E}'_{\text{CO}_2}$ observed during each of the first eight breaths after interruption of HFJV

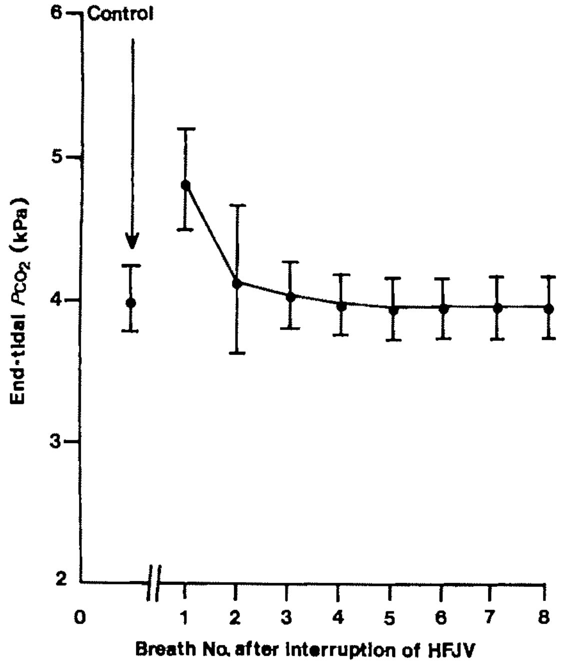

FIG. 3. Measurements of end-tidal $P\mathrm{co}_2$ recorded during each of the first eight breaths after interruption of HFJV with low frequency ventilation. Results are mean ± SD ($n = 36$ for breath numbers 1 to 6 and $n = 28$ breath numbers 7 and 8). The end-tidal $P\mathrm{co}_2$ during the first breath is significantly different from the control value ($P < 0.001$).

by large tidal volumes are shown in figure 3. There were no significant differences between the readings at 1, 3 and 5 Hz, so these have been combined. The $P\mathrm{E}'_{\mathrm{CO_2}}$ was significantly greater than the control values during the first breath ($P < 0.001$), variable in magnitude during the second breath and not significantly different from the control readings from the third breath onwards. Recordings of the expired carbon dioxide concentrations during the first three large breaths are shown in figure 4. The $P\mathrm{E}'_{\mathrm{CO_2}}$ recorded during the first breath after interruption of HFJV at all frequencies was 4.83 ± 0.35 kPa ($n = 35$). This was very similar to the measured arterial $P\mathrm{co}_2$ (4.96 ± 0.13 kPa; $n = 51$). However, by the third breath after the interruption of HFJV, the ($Pa_{\mathrm{CO_2}} - P\mathrm{E}'_{\mathrm{CO_2}}$) was restored and the two values were significantly different ($P < 0.001$). Figure 5 shows that ($Pa_{\mathrm{CO_2}} - P\mathrm{E}'_{\mathrm{CO_2}}$) at the third breath was similar at 1, 3 and 5 Hz, when the $Pa_{\mathrm{CO_2}}$ was in the normal range.

Second investigation

The total delay time of the carbon dioxide measuring system was 635 ms. This comprised a transit time of 300 ms and 0–95% capnograph response time of 335 ms. Recordings of the 5% carbon dioxide mixtures sampled as step changes

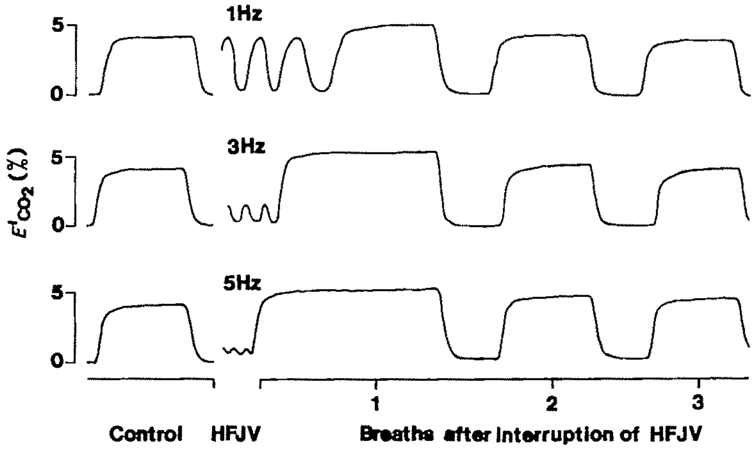

FIG. 4. Recordings of the end-tidal $P\mathrm{co}_2$ during the first three breaths after interruption of HFJV at 1, 3 and 5 Hz. The value of the end-tidal $P\mathrm{co}_2$ at the third breath is similar to the previous control value.

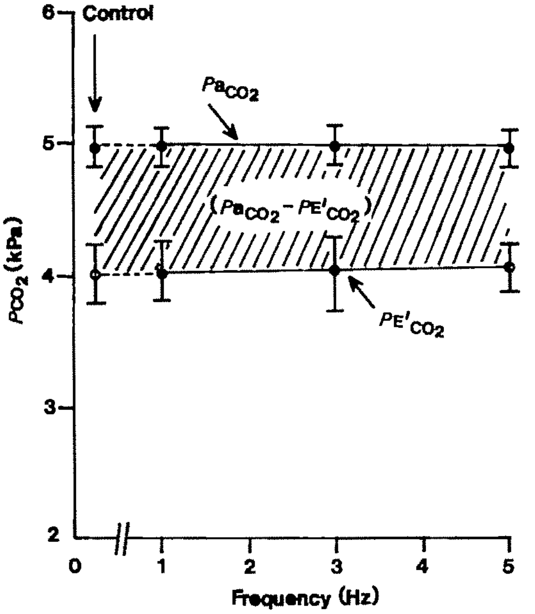

FIG. 5. Relationship between arterial and end-tidal $P\text{CO}_2$ measured during the third breath after interruption of HFJV at 1, 3 and 5 Hz. Results are mean ± SD. At every frequency the arterial and end-tidal $P\text{CO}_2$ values are significantly different ($P < 0.001$).

at 1, 3 and 5 Hz are shown in figure 6. The peak value of 5% carbon dioxide was observed only at 1 Hz, the readings at 3 Hz and 5 Hz being less than 5%. During the periods when the solenoid valve was closed and room air was sampled, the minimum value of carbon dioxide recorded was 0.4% at 1 Hz, increasing to 2.8% at 3 Hz, and 3.8% at 5 Hz. Although the presence of carbon dioxide during this phase could be attributable to incomplete diffusion of carbon dioxide away from the sampling site, the damped response at frequencies greater than 1 Hz suggests that the limited frequency response of the analyser may have contributed to the observed results.

DISCUSSION

Our results indicate that, during HFJV at 1, 3 and 5 Hz, the Pa_{CO_2} may be estimated from measurement of the $P\text{E}'_{\text{CO}_2}$ recorded during the first or third large breath.

When HFJV was interrupted with large tidal volume ventilation, we found that, during the first breath, Pa_{CO_2} and $P\text{E}'_{\text{CO}_2}$ were similar and independent of the frequency of HFJV (4.96 ± 0.13 and 4.83 ± 0.35 kPa, respectively). Similar observations were made by Mihm and co-workers (1982) in a study in dogs in which HFJV at frequencies of 1.7–15 Hz was interrupted with a single breath of 15 ml kg^{-1}, or greater. They found a strong positive correlation between Pa_{CO_2} and $P\text{E}'_{\text{CO}_2}$ ($r = 0.98$; $P < 0.001$) throughout the range of Pa_{CO_2} studied (3–10.7 kPa). Rearrangement of their linear regression equation yields the following relationship which may be used to predict the Pa_{CO_2}:

$$Pa_{\text{CO}_2} = 1.1\, P\text{E}'_{\text{CO}_2} - 0.3 \text{ kPa}$$

Applying this equation to our results gives a predicted mean Pa_{CO_2} of 4.99 ± 0.38, whereas the measured mean Pa_{CO_2} was 4.96 ± 0.13 ($n = 35$). This extrapolation from the two studies suggests that the technique may be applicable over a wide range of combinations of frequency and tidal volume.

Our results also show that $(Pa_{\text{CO}_2} - P\text{E}'_{\text{CO}_2})$ measured during the third normal volume breath after interruption of HFJV at 1, 3 or 5 Hz, was similar to that measured during a more prolonged period of ventilation at normal tidal volume and frequency. Thus it may be used to provide an

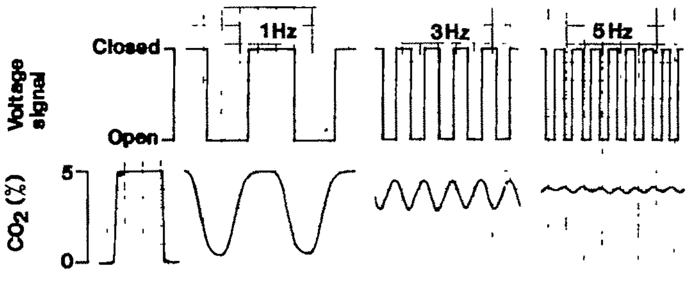

FIG. 6. Recordings of the relationship between solenoid valve frequency (upper recording) and 5% carbon dioxide sampled as step changes at 1, 3 and 5 Hz (lower recording). Only at 1 Hz is the peak 5% carbon dioxide observed.

alternative estimate of the Pa_{CO_2}. This confirms and extends the observation of Whitwam and colleagues (1983) at a frequency of 1 Hz.

The similarity between Pa_{CO_2} and $P\text{E}'_{CO_2}$ during the first large breath was unexpected and not easy to understand. Two possible explanations must be considered, the first being concerned with the altered timing and depth of ventilation, and the second associated with a possible alteration in the distribution of ventilation and blood flow.

It can be predicted that the rate of transfer of carbon dioxide from the pulmonary capillary blood to the alveolus will depend on the difference in partial pressure of carbon dioxide between the blood and gas, and will thus be influenced by the cyclical dilution of alveolar gas during inspiration (Dubois, Britt and Fenn, 1951). It is well known that the input of carbon dioxide to the lung (pulmonary capillary blood flow) is influenced by cardiac systole and by changes in lung volume associated with breathing, but that the variations in flow are not great when the subject is resting (Lee and Dubois, 1955). However, in the dog, approximately 250 ml of fresh gas is transferred into the 1000 ml of gas in the functional residual capacity at each breath. If this change were to occur instantaneously, the alveolar gas would be diluted by 25% (250/1000), that is from 6 kPa to 4.5 kPa. Although the degree of dilution is reduced by the fact that carbon dioxide continues to flow into the alveolus during inspiration, it is known that changes in the pattern of breathing can influence the carbon dioxide concentration in the alveolus and so influence the elimination of the carbon dioxide. For example, increasing the I:E ratio during mechanical ventilation decreases $(Pa_{CO_2} - P\text{E}'_{CO_2})$ and increases the efficiency of carbon dioxide elimination (Perez-Chada et al., 1983) whereas in exercise, when carbon dioxide production is very high, $(Pa_{CO_2} - P\text{E}'_{CO_2})$ may become negative (Jones, Robertson and Kane, 1979). High frequency jet ventilation results in a marked decrease in alveolar tidal volume so that the inspiratory dilution of alveolar gas is minimized, and it is possible that this may reduce $(Pa_{CO_2} - P\text{E}'_{CO_2})$ to values observed during the first breath. Although these time effects are probably of some importance, it is difficult to quantify their magnitude.

Another explanation for the existence of an increased $(Pa_{CO_2} - P\text{E}'_{CO_2})$ in anaesthesia is that there may be a zone of reduced perfusion in the non-dependent lung zones. Askrog (1966) has correlated the increase in $(Pa_{CO_2} - P\text{E}'_{CO_2})$ during anaesthesia with a decrease in pulmonary artery pressure. However, the magnitude of zone 1 depends on the relationship between alveolar pressure and pulmonary artery pressure, and it is conceivable that any reduction in mean alveolar pressure resulting from HFJV may decrease the number of poorly perfused alveoli and so may decrease alveolar deadspace. During this study, there were no significant differences in the relationship between mean airway pressure and mean pulmonary artery pressure at 1, 3 and 5 Hz.

The marked increase in $(Pa_{CO_2} - P\text{E}'_{CO_2})$ which was observed at 3 Hz and 5 Hz, has been reported previously with both open and closed ventilation circuits (Capan et al., 1981; Colgan, Teneyck and Sawa, 1983; Rolly and Versichelen, 1983). Various mechanisms have been suggested for this observation, including mismatching of ventilation and perfusion, mixing of inspired and expired gas in the airways, and inadequate capnograph response time. The results of our second study suggest that the last of these is the most important factor. It is concluded that the normal $(Pa_{CO_2} - P\text{E}'_{CO_2})$ is re-established by the third normal breath when HFJV at 1, 3 and 5 Hz is interrupted by ventilation at conventional frequencies and tidal volumes. Comparison with other studies suggests that this relationship may be maintained over a wide range of Pa_{CO_2}. Although the end-tidal plateau during the first breath is less reproducible than during the third breath, it appears to provide a close estimate of Pa_{CO_2}. However, it is important to determine whether this relationship is maintained in the diseased lung.

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EVALUATION OF CLOSED-LOOP CONTROL OF ARTERIAL PRESSURE AFTER CARDIOPULMONARY BYPASS

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SUMMARY

A closed loop computer system has been developed to deliver sodium nitroprusside (by infusion) to control systolic arterial pressure (SAP) after cardiopulmonary bypass. The performance of the closed-loop control system was evaluated by comparing nurse and computer control of SAP in 60 patients during the early postoperative period. The computer system provided better control of SAP than manual control by a member of the nursing staff.

Short-acting vasodilator agents, such as sodium nitroprusside (SNP), are used frequently to decrease arterial pressure after cardiac surgery. The reported benefits of such modulation of arterial pressure include protection from myocardial ischaemia (Roberts et al., 1977; Fremes et al., 1983) and reduced bleeding from suture lines (Viljoen, Estafanous and Tarazi, 1976). The standard method of controlling the administration of such agents is by making alterations to the rate at which the drug is infused—a task undertaken at the bedside by a member of the nursing staff. However, this can lead to poor control of arterial pressure because of:

(1) variation between patients in their responses to the vasodilator drug;
(2) alteration in the responses of individual patients with time;
(3) changes in the level of sedation or stimulation of the patient as, for example, after endotracheal suction;
(4) distraction of the nurse by other tasks which must be performed;
(5) nurse fatigue.

The use of a computer to monitor arterial pressure (measured via an intra-arterial cannula), calculate a suitable new infusion rate and direct a pump to deliver the new rate has been described by Sheppard, Kouchoukos and Shotts (1975) in patients after cardiac surgery. Their system was based on a central minicomputer which shared the processor time between all the patients in the intensive care unit: each patient's arterial pressure could be observed by the central computer for 6 s in each 1 min. An appropriate new rate of infusion was then calculated and delivered to the patient. The system functioned well, but was expensive and could not monitor each patient's arterial pressure continuously. Moreover, the infusion pump which delivered the vasodilator drug to the patient received only intermittent communication from the computer. In addition, the failure of a single component in the central computer could interfere with the functioning of the entire system.

PATIENTS AND METHODS

Materials

The arterial pressure closed-loop control system developed at Glasgow Royal Infirmary is based on an Apple IIe microcomputer. Cardiovascular data were obtained from a Kone 565A monitor and the infusion was delivered via a dedicated catheter inserted to the internal jugular vein, by an Imed 929 computer-controlled pump (fig. 1). The cost of the computer system and infusion pump was approximately £3000.00.

The intra-arterial pressure waveform is analysed using an 8-bit analogue to digital convertor (ADC, Interactive Structures AI02). This is controlled by clock interrupts (Thunderclock

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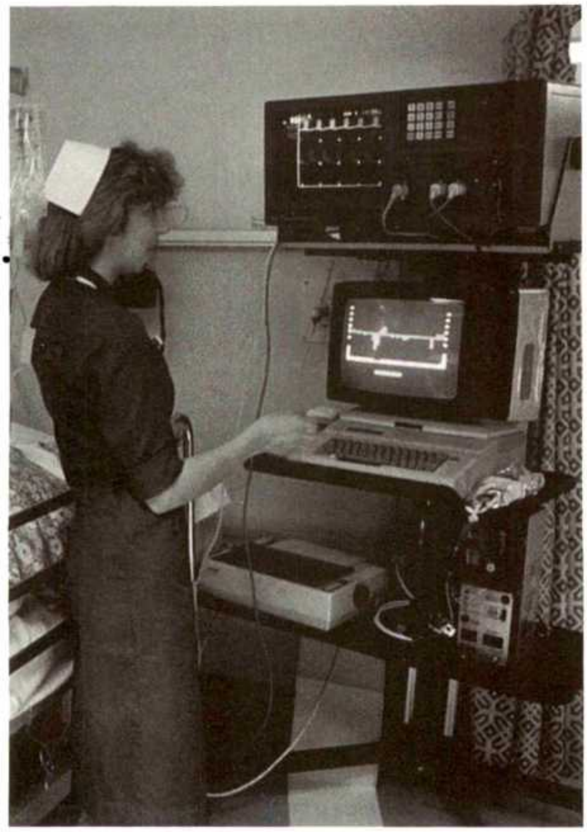


FIG. 1. Closed-loop computer system for the control of systemic arterial pressure.

Plus, Thunderware Inc.) to obtain 256 samples per second. A machine code subroutine analyses the digitized data beat by beat as a background task and places the required information in memory where it is read by the main application program. Communication between the Imed 929 infusion pump is arranged by passing the relevant command strings into a machine code subroutine which handles data transfer and the necessary software handshaking (Kenny et al., 1985).

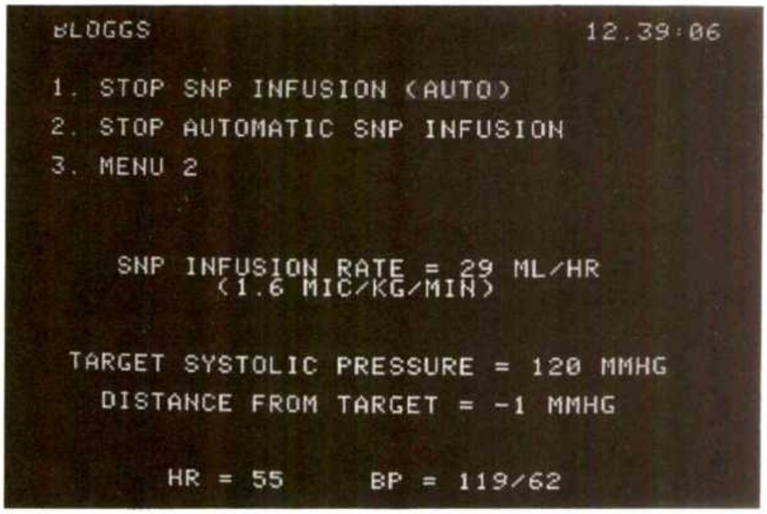
The main application program was written in BASIC and then compiled; the compiled code occupies approximately 30K bytes of memory.

The program consists of four major sections:

(1) arterial pressure data collection and verification;
(2) control algorithm;
(3) infusion pump subroutine;
(4) user interface.

Arterial pressure data collection and verification. Values for systolic and diastolic arterial pressures and heart rate are obtained from the machine code subroutine which analyses the arterial waveform. If a satisfactory waveform has not been detected by the subroutine, an error flag is set which the BASIC program interprets. When an error is detected the ADC is read and, if the pressure is less than 20 mm Hg, an audible alarm is given and a message that the transducer is being zeroed is displayed. If the pressure is greater than 220 mm Hg, the message displayed is that a flush has been detected. An intermediate pressure, as would occur during sampling from the arterial line, generates the message that a valid waveform cannot be obtained. Damping of the waveform is detected using the criteria suggested by Raison and colleagues (1968). Artefacts caused by mechanical disturbance of the manometer tubing are detected by comparing the systolic and diastolic pressures and heart rate for each beat with the previous acceptable beat. Mechanical disturbance causes sudden changes in rate and pressures which are, therefore, rejected. A 3-s period is allowed for stabilization and, if subsequent analysis does not produce acceptable values, audible and visual warnings are given. If an error in verification of the arterial waveform occurs, the rate of SNP infusion is reduced by 25% until the fault is corrected.

Control algorithm. The control algorithm was based on the proportional-integral-derivative controller developed by Sheppard and Kouchoukos (1977) and modified by Slate (1980). Modifications involved increasing the frequency of observation to include every beat (except during disc operations or printing, when interrupts have to be disabled) and provision to alter the review time from 1 min upwards before the calculation of a new infusion rate. In addition, a "tracking" facility is incorporated which examines the arterial pressure after (review time/2 × 60s). If the change in pressure is greater or less than predicted, a further alteration in infusion rate is calculated before the next review time. The effect of this is to allow more frequent alterations to the infusion rate, depending on the response by the patient. The new calculated infusion rate produced by the algorithm is corrected for weight, averaged with the previous rate and the resulting value used for the next period. These modifications were found to minimize oscillations in the control of arterial pressure.



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BLOGGS                              12.39:06

1. STOP SNP INFUSION (AUTO)
2. STOP AUTOMATIC SNP INFUSION
3. MENU 2


     SNP INFUSION RATE = 29 ML/HR
         (1.6 MIC/KG/MIN)

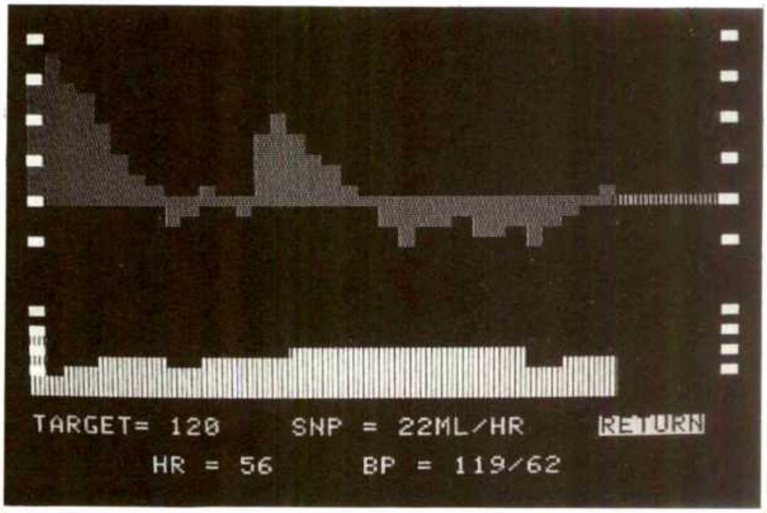

  TARGET SYSTOLIC PRESSURE = 120 MMHG
    DISTANCE FROM TARGET = -1 MMHG


        HR = 55       BP = 119/62
```

FIG. 2. First screen page displaying the menu from which the system is controlled.

Infusion pump subroutine. During the infusion of SNP, the control system requires correct data communication between the computer and the infusion pump every 22 s. This is an essential safety feature for apparatus which is to be used routinely by non-technical personnel, since failure of either component should be detected quickly and an appropriate alarm sounded.

User interface. The control system has been developed with ease of nurse operation and clarity of display as principal features. Three screen pages are available: page 1 allows control of the system (fig. 2). Key number 1 stops immediately delivery of SNP to the patient. Pressing the number 2 key changes control from advisory to automatic mode and *vice versa*. Key 3 displays the second menu page which allows options such as alterations of the target pressure, concentration of



```
TARGET= 120     SNP = 22ML/HR
     HR = 56       BP = 119/62
```

FIG. 3. The upper graph shows the distance from the target pressure of the SAP at each alteration of the SNP infusion rate. The upper scale markings represent −10, 0, 10, 20, 30 and 40 mm Hg from the target pressure. The lower graph shows the infusion rate of SNP; scale markings are 1, 2, 3 and 4 μg kg^{-1} min^{-1}.

TABLE I. *Average midpoint and range prescribed, duration of study and maximum rate of SNP infusion (mean ± SD)*

	Group I Nurse control	Group II Computer control
Mid point (mm Hg)	112.8 ± 4.25	112.9 ± 4.25
Range (mm Hg)	41.0 ± 8.75	40.5 ± 9.22
Duration of study (min)	145.0 ± 24.30	157.0 ± 26.90
Maximum rate of SNP infusion ($\mu g\ kg^{-1}\ min$)	2.80 ± 1.98	3.85 ± 4.05

SNP, and display of the colour trend graph to be selected. The upper part of the trend display (fig. 3) shows the nurse at the bedside how far the patient's systolic arterial pressure varies from the target pressure and the lower part shows the delivery of SNP in micrograms per kilogram per minute.

A further feature of the software is the possibility of using the system in advisory or automatic mode. When used in advisory mode, the computer will display the newly calculated infusion rate which can be altered as the operator considers appropriate. This mode is used normally only when the system is connected initially to a patient (before proceeding to automatic control), but could be used continuously if required.

For all patients in the cardiac intensive care unit, the surgical staff prescribe routinely a range within which the patient's systolic arterial pressure must be maintained. The surgical staff consider that systolic pressures outside this range are harmful. If a patient's systolic pressure lies consistently outside the prescribed range, the surgical staff should be notified to allow revision of the drug and fluid therapy. The systolic pressure ranges prescribed varied according to the patient's preoperative systolic pressure and surgical opinion and are shown in table I. In the case of an increasing systolic pressure, the decision to increase or commence SNP infusion should be made on noting the upward trend before the systolic pressure is above the upper limit of the prescribed range. For this reason the nursing staff choose narrower pressure limits, such as 110–120 mm Hg, outside which the trend of systolic pressure is monitored closely to decide the appropriate time to commence or alter SNP therapy.

Patients

The close-loop control system was evaluated by studying 60 patients who required sodium nitroprusside by infusion for a minimum of 2 h after cardiac surgery. The patients were allocated randomly to have their arterial pressures controlled by nurses ($n = 30$) or by the closed-loop computer system ($n = 30$). The nurses were either qualified and undergoing training in intensive care or were experienced sisters who worked full-time in the cardiac intensive care unit. The computer program was designed to aim for the midpoint of the range prescribed by the surgical staff. Systolic arterial pressure and the rate of SNP infusion were recorded at intervals of 1 min from each patient, manually in the nurse-controlled group and automatically in the computer-controlled group. Analgesia and sedation were provided by the administration i.v. of morphine and midazolam; bolus doses were given as determined by the nursing staff.

RESULTS

There were no statistical differences between the groups in age, sex, surgical procedure or weight. There were no significant differences between the mid-points and ranges prescribed, duration of

TABLE II. *Average per cent time outside pressure range, groups I and II*

Range		Range ± 10 mm Hg		Range ± 20 mm Hg		Range ± 30 mm Hg	
I	II	I	II	I	II	I	II
27.69	8.77	10.47	2.48	2.93	0.741	1.57	0.224
$P < 0.00003$		$P < 0.0003$		$P < 0.01$		$P < 0.05$	

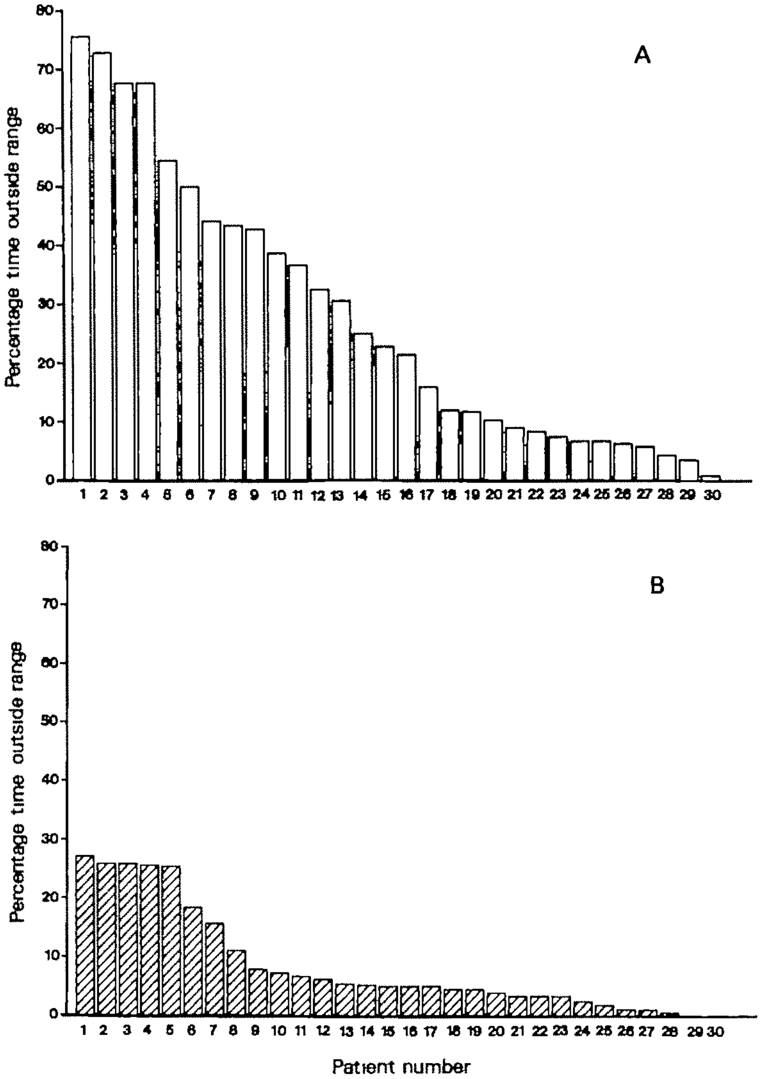


FIG. 4 A: Percentage time spent outside the prescribed systolic pressure range for each of the 30 patients whose systolic arterial pressure was controlled by the nurse. B: Percentage time spent outside the prescribed systolic pressure range for each of the 30 patients whose systolic arterial pressure was controlled by computer.

study or the maximum rate of SNP infusion in the two groups (table I). Each study began when the patient was given SNP in the intensive care unit. Before the SNP infusion was started 11 patients (37%) in the nurse group and 12 patients (40%) in the computer group had a systolic arterial pressure outside the prescribed range, but there was no significant difference between the two groups.

The results are expressed as the percentage time spent outside the prescribed range for each patient. The data were analysed using a two-tailed Mann–Whitney *U* test for the percentage time spent outside the range in total, outside the range ±10 mm Hg, ±20 mm Hg and ±30 mm Hg (table II).

Figure 4A shows the percentage time spent outside the prescribed systolic pressure range for each of the 30 patients in the nurse-controlled group. Sixteen of the 30 patients spent more than 20% of the time outside the pressure range prescribed. In comparison, figure 4B shows the

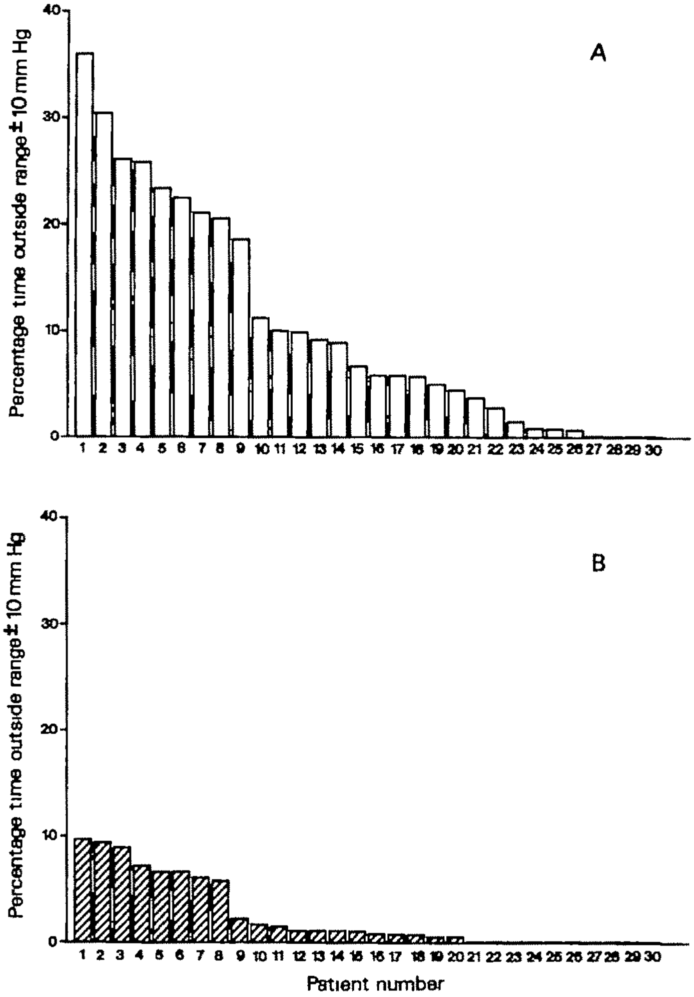


FIG. 5. A: Percentage time spent outside the prescribed systolic pressure range ±10 mm Hg for each of the 30 patients in the nurse-controlled group. B: Percentage time spent outside the prescribed systolic pressure range ±10 mm Hg for the 30 patients in the computer-controlled group.

same information for the computer-controlled group. Five out of 30 patients spent more than 20% time observed outside the pressure range.

Figures 5A and 5B show the percentage time spent outside the prescribed pressure range ±10 mm Hg for each of the 30 patients belonging to the two groups. In the nurse-controlled group, 10 patients out of 30 spent more than 10% of the time outside the systolic pressure range ± 10 mm Hg. Nineteen out of 30 spent more than 5% of the time observed outside the range ± 10 mm Hg. In comparison, no patient in the computer group spent more than 10% of the time observed outside the range ±10 mm Hg, while eight of 30 patients spent more than 5% of the time observed outside the pressure range ±10 mm Hg.

Figures 6A and 6B show the percentage times spent outside the prescribed range ±20 mm Hg for the nurse- and computer-controlled groups, respectively. In figure 6A, four of the 30 nurse-controlled patients spent more than 10% of the time outside the prescribed range ±20 mm Hg; while in figure 6B only one patient controlled by the computer system can be seen to have sent more than 5% outside the range ±20 mm Hg.

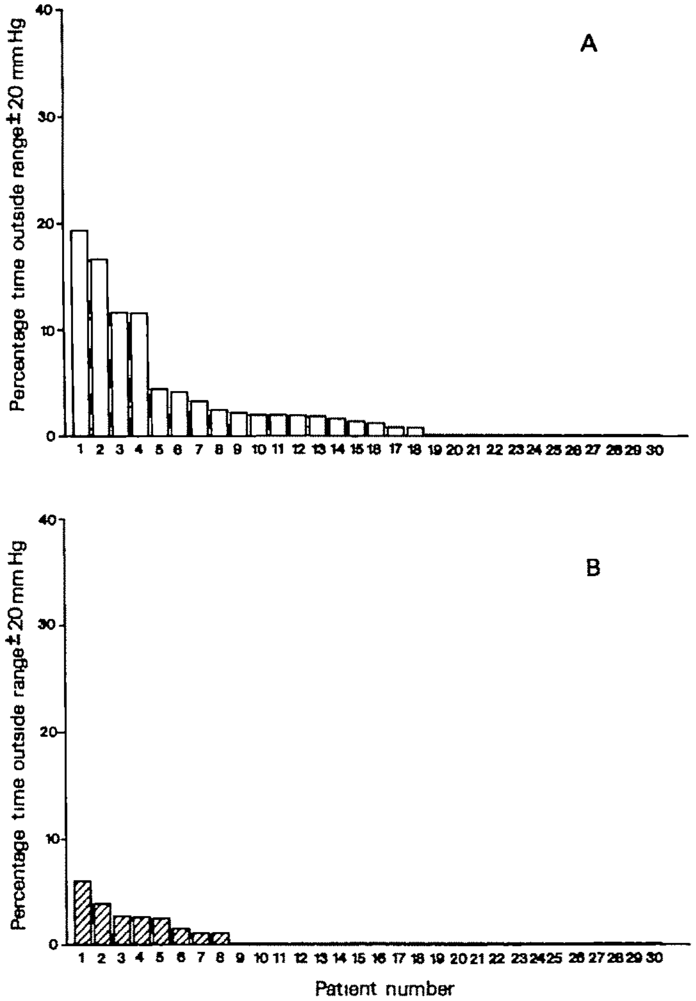


FIG. 6. A: Percentage time spent outside the prescribed systolic pressure range ±20 mm Hg for the 30 patients in the nurse-controlled group. B: Percentage time spent outside the prescribed systolic pressure range ±20 mm Hg for the 30 patients in the computer-controlled group.

DISCUSSION

The difficulty of assessing a closed-loop arterial pressure control system with manual control has been stressed by Potter and colleagues (1984), but Sheppard and colleagues (1981) compared nine patients who had undergone cardiopulmonary bypass and in whom mean arterial pressure (MAP) was controlled by computer, with seven patients who received conventional manual control. Measurements were made for each patient at 5-min intervals for 8 h and the results showed that computer control was better than manual control. De Asla and colleagues (1985) compared the effectiveness of the manual control of MAP in 37 patients with computer control in 49 patients. They reported the computer system to be superior to the manual. However, measurements were made at 5-min intervals for each hour and the average of the 12 measurements was defined as the hourly average arterial pressure and compared with the target pressure. Such hourly averages may fail to represent true variations in pressure. Hammond, Kirkendall and Calfee (1979) used the computer-controlled administration of SNP to manage hypertensive crises successfully in 12 patients. They also used MAP as the input signal to the control algorithm. Control of patient's

MAP was achieved initially by the nurses and, thereafter, maintained by the computer system. Petre, Cosgrove and Estafanous (1983) reported the results of a closed-loop computer system which controlled MAP after cardiac surgery. After stabilization for 20 min, 47 of 57 patients (82.5%) had at least 75% of their pressure readings within the range of the target mean pressure ±20%. This compares with only 16 of 57 patients (28%) during the period of stabilization.

In all these studies, the closed-loop system was required to control MAP which tends to have less inherent variation than systolic arterial pressure. In our study, systolic arterial pressure was the input signal and was recorded every 1 min to detect transient alterations. Control within the ranges prescribed for each patient by the surgical staff was not achieved before the studies were begun. Ninety-one per cent of the pressure recordings in our study were within their prescribed ranges (mean target systolic pressure = 113 mm Hg ± 18%). This compares favourably with the results reported by Petre and his colleagues (1983).

The aim of our study was to determine whether computer control of SNP infusion could fulfill the prescription of the cardiac surgical staff better than the established routine method of nurse control. The computer system was clearly demonstrated to achieve the desired control better than the nursing staff. One possible explanation is that the computer was programmed to alter the infusion rate of SNP when the systemic pressure deviated from the mid-point of the prescribed range, whereas the nursing staff may have been inclined to alter the infusion rate only when the pressure was close to the limits prescribed, and so be more likely to overshoot. However, in practice, the nursing staff were aware that the prescribed ranges were strict limits which should not have been exceeded. Therefore, they selected narrower ranges since these allowed them to intervene before the prescribed limits were exceeded. In addition, if the aim of the nurses had been merely to control around the prescribed limits, we would have expected extremes of pressure to have been much better controlled by the nurses. This was not the case, since the average percentage times spent outside the range ±10 mm Hg, ±20 mm Hg and ±30 mm Hg were all greater for nurse control than for computer control. Since the optimum target systolic pressure was not known for each patient, the surgical staff considered it inappropriate to request the nurses to undertake the time-consuming task of maintaining the systolic pressure at a specific target. This would have caused them to neglect other nursing duties. We, therefore, compared the computer-controlled system with the standard practice in the cardiac intensive care unit.

The closed-loop computer system controlled the patient's systolic arterial pressures within narrower ranges than the nurses could achieve. As Fremes and his colleagues (1983) have pointed out, myocardial ischaemia may be caused by arterial pressures that are increased or inappropriately decreased for the individual patient. Thus close supervision of the SNP infusion rate is essential for good control of arterial pressure. Further studies are required to evaluate the clinical significance of improved arterial pressure control in relation to morbidity and mortality.

This is not to suggest that a closed-loop system should ever replace the experienced nurse at the bedside. We view the computer control system as analogous to the improvement in control which is achieved by using a volumetric infusion pump compared with the standard i.v. administration set. The computer system can only be used as an aid, since the nurse must have the final responsibility for supervision of drug delivery. Provided with a clear, coloured graphic display of the patient's response to the infusion of vasodilator, the nurse can have an immediate appreciation of the situation.

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AN ACOUSTIC MODEL OF THE PATIENT UNDERGOING ARTIFICIAL VENTILATION

E. S. LIN AND B. E. SMITH

SUMMARY

The difficulty of applying conventional concepts of respiratory mechanics to high frequency ventilation (HFV) has so far inhibited its general acceptance by clinicians. The basis of an approach derived from an acoustic analysis of the ventilated patient is presented which may help to clarify the mechanism of action of HFV and offer some guidelines to its clinical application. The ventilator is considered as an acoustic source, and the patient's acoustic response to the ventilator is analysed. A response equation for the patient's respiratory system at low frequencies is derived, from which an expression for the fundamental resonant frequency is obtained. The high frequency acoustic response of the patient is examined with particular reference to the possibility of exciting multiple resonant modes within the airways. Following this, we have discussed the significance of the acoustic response and acoustic resonance in relation to gas exchange. It is suggested that these resonances may be used in adjusting indices of HFV in order to obtain optimum ventilation.

In conventional intermittent positive pressure ventilation, respiratory gas exchange can be considered in terms of the bulk movement of gas into and out of the lungs. However, in high frequency ventilation (HFV) it is difficult to apply this concept, as the tidal volumes may be significantly less than the anatomical deadspace of the lungs. In order to clarify the mechanism by which gas exchange occurs in HFV, studies have been made of the distribution of inspired gas flow in the lungs (Fredberg and Mead, 1979; Michaelson, Grossman and Peters, 1975). In addition, models have been proposed (Fredberg, 1980; Scherer and Haselton, 1982) to explain the transport of gases between the alveolar regions and the airways containing fresh inspired gas.

Although these models contribute to the understanding of the mechanism of gas exchange when ventilating at high frequencies, it would be difficult to use them as a guide when applying HFV clinically. Although conventional models work well at the ventilation frequencies used normally, a totally new model is required at high frequencies.

Acoustics as applied to a ventilated patient

Any vibrational disturbance in a given medium obeys well established physical laws which have been studied classically in the field of acoustics. A disturbance in this context refers to any bulk displacement of atoms or molecules in the medium from their normal equilibrium position by an externally applied force. Alternatively, the medium's behaviour may be considered in terms of "particles" or elemental volumes, which may be disturbed from their equilibrium positions. Such disturbances may be transmitted in the form of an "acoustic wave". Hence, the effects produced by a pressure pulse or train of pulses in a gas or fluid may be analysed by considering the behaviour of acoustic waves. Acoustic waves are characterized by indices such as frequency, wavelength and velocity of propagation and, within a narrow frequency band (30 Hz–20 kHz), are responsible for the sensory phenomenon of hearing.

The following discussion considers a patient receiving mechanical ventilation as an acoustic system in which a source of acoustic waves (the ventilator) radiates into an acoustic load (the patient and ambient surroundings).

The ventilator as an acoustic source

The simple system shown in figure 1 illustrates that any ventilator acts as a source of acoustic

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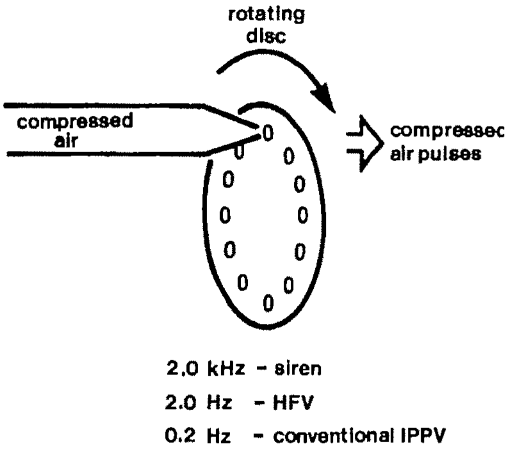

FIG. 1. Diagram showing how a spinning disc interrupting a compressed air jet may form the basis of a ventilator or simple acoustic source.

waves. It consists of an air jet interrupted by a spinning disc to produce a train of pulses. This mechanism is similar to that of a familiar acoustic source, the early air raid warning siren (Clark-Jones, 1946). However, by changing the frequency of operation, such a mechanism could, in principle, form the basis of either a conventional or a high frequency ventilator.

The acoustic output of a ventilator can be characterized by the frequency–power spectrum of the pressure waveform produced. Two examples of pressure waveforms and their corresponding power spectra are shown in figure 2. These illustrate (*a*) that if the pressure waveform is sinusoidal all the acoustic power occurs at a single frequency, and (*b*) that, in the case of a square wave, power exists at several harmonics as well as at the fundamental frequency.

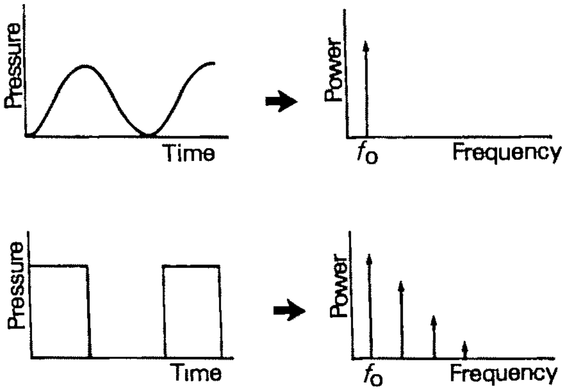

FIG. 2. Frequency–power spectra for an ideal sinusoidal pressure waveform, or rectangular pressure waveform.

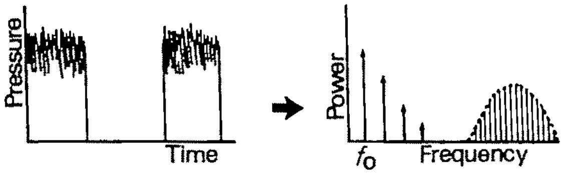

FIG. 3. Frequency–power spectrum for high frequency jet ventilation pulses.

Further modification of the acoustic power spectrum ultimately presented to the patient's respiratory system may occur at the interface used between the ventilator and the patient. If the ventilator delivers gas to the patient through a jet cannula, as in high frequency jet ventilation (HFJV), this acts as an additional source of noise at frequencies in the kHz range (Smith, 1986) (fig. 3).

Considerations of acoustic wavelength

An important relationship in the analysis of any acoustic system is the ratio of the acoustic wavelengths involved to the physical dimensions of the system. Each acoustic frequency is associated with a specific wavelength determined by the relationship $v = f\lambda$ where v = velocity of sound, f = frequency, and λ = wavelength. Some examples are shown in table I. From these values it can be seen that, when comparing wavelengths to the dimensions (d) of the system (that is, patient and ventilator), two distinct situations emerge. The first arises when the wavelengths are very much greater than the overall dimensions of the system, that is $\lambda \gg d$. This occurs at fundamental ventilation frequencies (0.2–2 Hz). In contrast, at higher frequencies (20 kHz) which may be generated by a jet cannula, the relationship $\lambda \ll d$, is more applicable.

A simple model for the ventilated patient at fundamental ventilation frequencies ($\lambda \gg$ d). An acoustic wave produces pressure variations in both time and space. However, in a system in which the

TABLE I. *Fundamental ventilation frequencies* (f), *and corresponding acoustic wavelengths in air* (λ), *with the relationship of wavelength to system dimensions* (d)

Frequency	Wavelength (m)	$\lambda : d$
0.2 Hz	1700	$\lambda \gg d$
2 Hz	170	$\lambda \gg d$
20 kHz	0.017	$\lambda \ll d$

acoustic wavelengths are much greater than the dimensions of the system, the spatial variation of pressure becomes non-significant and the system is effectively subject to a time variant pressure signal only. Thus at low frequencies (where $\lambda \gg d$) the analysis of a system's acoustic response is simplified in that a "lumped element" approach can be used (Kinsler and Frey, 1962). At conventional ventilation frequencies this results in the valid use of the compliance and resistance model. However, at high frequencies, inertia must be taken into account and this introduces the possibility of resonance. A simple model representing the respiratory system of a patient is shown in figure 4 and this has been used to analyse the acoustic response of the patient at fundamental ventilation frequencies. This model consists of the compliant volume of the thorax being driven by a force produced by the ventilator, via the air column in the conducting airways. This vibrates the air column axially like a piston in a cylinder. Using this model, an expression for the resonant frequency, f_0, of the respiratory system can be derived (Appendix 1):

$$f_0 = \frac{1}{2\pi}\sqrt{\frac{S}{L.C.\rho}}$$

where

L = effective length of the upper airway

S = effective cross-section of the upper airway

ρ = density of gas

C = thoracic compliance.

Taking typical values, an approximate figure for the resonant frequency for the adult respiratory system may be obtained:

$$L = 0.15\ \mathrm{m}$$

$$S = 0.00018\ \mathrm{m}^2$$

$$\rho = 1.3\ \mathrm{kg\ m}^{-3}$$

$$C = 100\ \mathrm{ml/cm\ H_2O} = 10^{-6}\ \mathrm{m}^{-5}\mathrm{N}^{-1}$$

$f_0 = 5$ Hz or, in terms of breaths per minute: = 300 b.p.m.

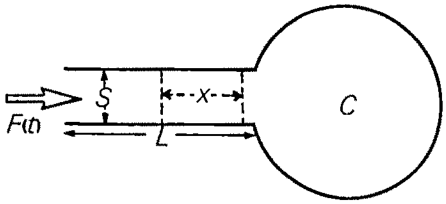

FIG. 4. Simple model used in the derivation of the low frequency acoustic response of the respiratory system. $F(t)$ = driving force from ventilator, C = compliance of thoracic volume, S = effective cross-sectional area of upper airway, L = effective length of upper airway, x = axial displacement of gas in airway.

Perhaps of more practical value than the absolute values for resonant frequency, are the simple relationships between f_0 and L, S and C. Acoustically, the rigid tube in the above model could also include connections between the ventilator and the patient, and thus, the relationship:

$$f_0 \alpha \sqrt{\frac{S}{L}}$$

will apply, not only to variations in individual anatomy, but also to the dimensions of the connecting pipes which may become significant in their effect on the resonant frequency of the system.

Similarly, the relationship:

$$f_0 \alpha \sqrt{\frac{1}{C}}$$

gives a guide as to how resonant frequency will vary with thoracic compliance, and possibly how ventilation frequencies should be varied if compliance changes.

The response of the patient's respiratory system to high frequencies ($\lambda \ll d$). As discussed above, a ventilator, if interfaced to the patient using a jet cannula, produces high frequency components extending the frequency range of the acoustic output into the upper audio range. At these frequencies the wavelengths are small compared with the dimensions of the system ($\lambda \ll d$). In this case, analysis of the response of the system involves examining the way in which acoustic waves propagate throughout the respiratory tract. At these frequencies local resonances may be excited within the airways themselves. The production of such resonances will be dependent on the changes in acoustic impedance (Appendix 2) seen by the waves as they travel through the airways. Where there are changes in acoustic impedance, partial reflection of the acoustic waves will take place and lead to the formation of standing waves. Changes in impedance will occur with any alteration in the geometry of the airway and, in particular, where there is a change in cross-section or branching.

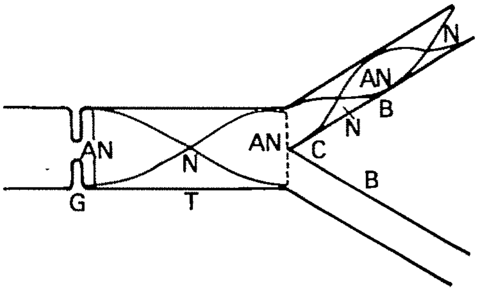

FIG. 5. Diagram showing fundamental resonance in trachea between glottis and carina with antinodes (AN) and node (N).

An example would be the fundamental mode for the trachea between the glottis and the carina (fig. 5). Given that the acoustic impedances are fairly closely matched, since the sum of the cross-sectional areas of the bronchi is similar to the cross-section of the trachea, the fundamental resonant mode will be similar to that in an open-ended pipe. Thus the resonant frequency, f_0, is given by:

$$f_0 = \frac{a}{2L}$$

where a = velocity of sound, L = length of trachea.

Taking typical values for an adult, we obtain a resonant frequency for the trachea of:

$$f_0 = 1100 \text{ Hz}$$

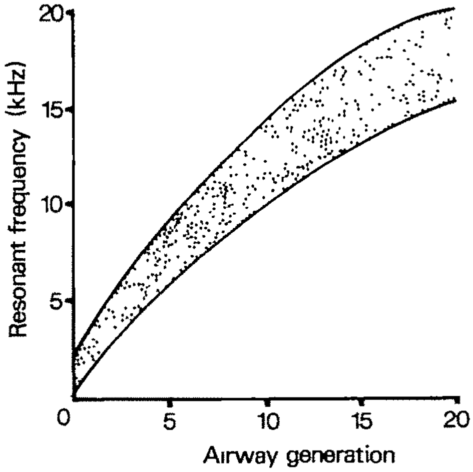

FIG. 6. Estimated resonant frequencies for successive generations of airways in the respiratory system.

As we move down the respiratory tract, decreasing lengths of airway will occur between successive branches and the resonant frequency of the standing waves formed will increase (fig. 6). Such frequencies may be generated by cannulae typically used in HFJV (Smith, 1986) (fig. 7).

DISCUSSION

The preceding acoustic analysis demonstrates two main points. First, it shows that the resonant frequency of the respiratory system as a whole can be derived from a simplified theory. This frequency, as discussed below, is in rough agreement with the optimum frequency for ventilation observed by other workers. Second, it shows again with simplified theory, that local resonances can be expected at much higher frequencies and that frequencies in this range are generated by jet ventilators.

At low frequencies it is assumed that the ventilator–patient combination behaves as a linear system in response to acoustic signals. This is valid where limited gas flow rates and tidal volumes are involved as in high frequency oscillation, but is less so at the higher tidal volumes and flow rates used in other forms of HFV. The lumped element expressions obtained for the inertance and resistance coefficients in the response equation (a) (Appendix 1) also depend on the nature of the flow velocity profiles in the airways. Correction of the flow resistance is discussed later; however, this should not significantly affect the value for the resonant frequency at low frequencies. The inertance may be corrected by a factor which assumes a value between 1.0 and 1.33 as the velocity profile in the airway varies from plane to parabolic in shape (Van Den Berg, 1960). However, bearing the preceding limitations in mind, a qualitative discussion based on the above model still remains valid in describing the acoustic response of the system, and can offer some guidance in practical situations.

In the high frequency model, the resonant frequency of a given rigid tube is calculated quite simply as shown earlier, but this is only an approximation to the real situation of intra-airway resonance which will be affected by many factors, including the following:

(i) Compliance of the airway walls.

(ii) Variation of the velocity of propagation in the tube with radius of the tube. The velocity decreases with radius and wavelength.

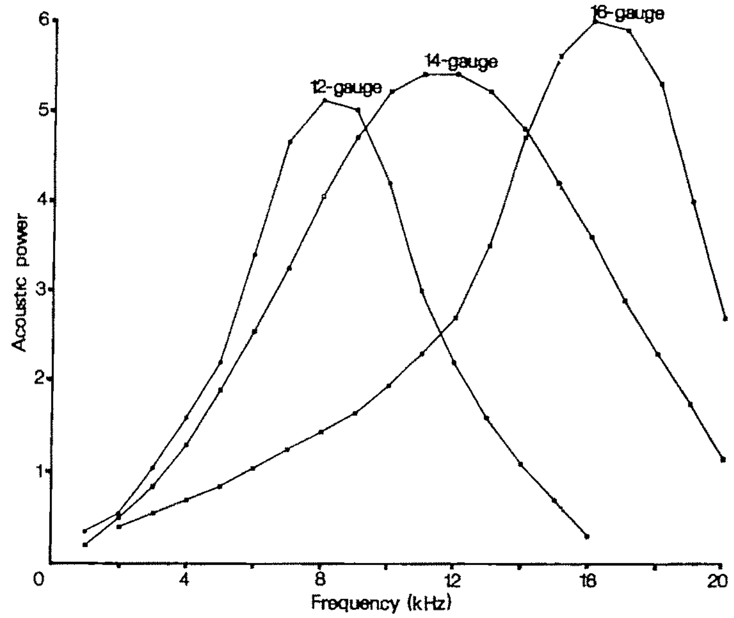

FIG. 7. Measured acoustic frequency spectra for three different sizes of cannulae used in a practical HFJV system (Smith, 1986).

(iii) Variation of velocity of propagation with pressure or composition of gas in the tube.
(iv) Decrease in velocity of propagation with irregularities or contained matter (secretions).

The low frequency model

The representation of a ventilated patient as a simple mechanical oscillator at low frequencies carries certain implications. The periodic motion of a mechanical oscillator is associated with an interconversion of kinetic and potential energy. In the case of a simple pendulum, this interchange occurs between the velocity of the bob and its height. In the above model the interchange occurs between the inertance and compliance elements. When the system is left to oscillate, this interconversion of energy will occur at a frequency determined by the elements in the system; that is, its resonant frequency. However when a periodic force is applied to the system, as when a patient's lungs are ventilated, the response will be determined by the driving and resonant frequencies. In this case forced oscillations are said to be taking place. In order to produce oscillations, a continuous energy input is required. However, as the driving frequency, f, approaches the resonant or natural frequency, f_0, of the system, the magnitude of the response for a given input will increase to a maximum (fig. 8). This can also be derived mathematically from equation (c) in Appendix 1.

Thus the response to a given input is a maximum at f_0 (curve A), or alternatively, the input amplitude required to produce a given response will be a minimum at f_0 (curve B).

The relationship between the mechanical behaviour of the patient's respiratory system and gas exchange may be related to two possible mechanisms. First, increased movement of the chest wall may facilitate bulk gas mixing within the lungs. Second, the tidal volumes attained will be related to the amplitude of the excursions of the chest wall. At resonance the mechanical response is maximal for a given energy input as reflected by baseline to peak airway pressures. Therefore, at resonance the effect of these mechanisms on gas exchange could be maximum for minimum airway pressures.

HFV studies in animals have suggested the existence of an optimum frequency for ventilation as reflected by the steady state Pa_{CO_2}. This has been found to be in the region of 20 Hz using rabbits with oleic acid-induced lung disease (Wright et al., 1981). Work with dogs using

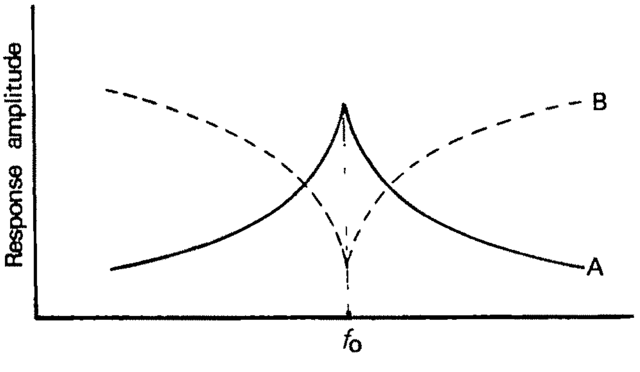

FIG. 8. Output and input variation with frequency in a resonant system. Curve A: output amplitude plotted against frequency for a constant input amplitude. Curve B: input amplitude required to produce a given output amplitude.

measurements of steady state Pa_{CO_2} yielded a value for optimum ventilation frequency of 15 Hz (Bohn et al., 1980). In man, it has been found that short term carbon dioxide removal at constant tidal volume (VT), increased with frequency up to about 5 Hz and then remained stable or decreased (Goldstein et al., 1981). In an HFV study of six ventilator-dependent patients with neuromuscular disease (Rossing et al., 1981), assessments of the effectiveness of ventilation suggested an optimum range of ventilatory frequencies of between 200 and 500 b.p.m. (3.3–8.3 Hz). Drazen, Kamm and Slutsky (1984) concluded in their extensive review of HFV: "...in most species studied there is a frequency above which $\dot{V}CO_2$ no longer increases or may even decrease at a fixed VT. This is > 25 Hz in normal dogs and $\simeq$ 5 Hz in normal humans."

Damping factors

The effect of damping in the system is represented mathematically by the coefficient K_r in Appendix 1, equation (c), and can affect the response curve as shown in figure 9.

In practice, damping is caused by the resistive elements in the system and represents elements in which energy is dissipated rather than being stored as in the inertance or compliance elements. Thus an increase in resistance leads to an increase in damping. The resistive element includes the following factors:

(i) Resistance to gas flow in the airways.
(ii) Viscous and frictional forces in the expansion of the thorax and airways.
(ii) Acoustic radiation resistance seen by the acoustic signals emitted from the large airways and the radiation resistance seen by the chest wall as it moves.

In the simple analysis of the system described above the resistance to flow in the airways is taken to be independent of frequency but, in practice, it has been found that this factor is frequency dependent (Finucaine et al., 1975). This effect is the result of the non-parabolic velocity profiles obtained with periodic flows, and could increase flow resistance by 30% from the value at steady flow.

Damping is of practical significance as a possible hazard exists at resonance. When the system is driven at the resonant frequency, if the system damping is inadequate, the maximizing of intrapulmonary gas dynamics might become harmful to

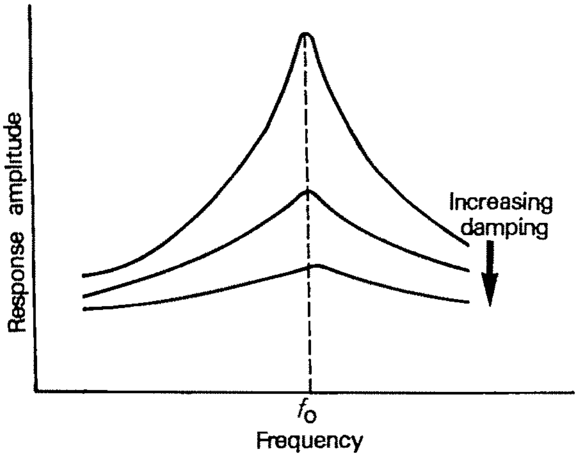

FIG. 9. The effect of damping on the frequency response of a resonant system.

the patient. In HFV the energy delivered to the system is dependent on the driving pressure and the inspiratory period. Thus, to control the amplitude of the response at resonance these variables should be decreased accordingly.

Initial work with animal models suggests that, at low frequencies, the system is heavily damped, limiting the Q factor to 2 or less at resonance (Smith and Lin, in preparation).

The high frequency model

Consideration of the acoustic response of the conducting airways suggests that multiple resonant modes could be excited by a suitable acoustic input. The occurrence of such multiple resonant modes is supported by work with computer models simulating branching airway networks (Fredberg and Hoenig, 1978), and isolated canine lung preparations (Fredberg et al., 1978). The precise role of acoustic resonance within the conducting airways in gas mixing and, hence, gas exchange has yet to be quantified. The production of resonance in a tube is associated with considerable agitation of the gas in the tube. It has been shown in preliminary experiments (Smith, 1986), that the rate of mixing of carbon dioxide and air in a closed tube is increased significantly by application of a frequency close to the resonant frequency of the system. Certainly, bulk flow of gas in resonating tubes occurs (Rayleigh, 1883). Rayleigh concluded that mean motion of the gas in the tube occurred at resonance from the antinodes to the nodes close to the walls of the tube, and returned axially in the opposite direction. In the same period, Dvŏrák (1878) observed another phenomenon in air resonators which could be significant in affecting bulk flow of gas in an air resonator. This was the production of a mean pressure greater than atmospheric pressure inside the resonator during resonance. The excess pressure was enough to cause movement of the resonator itself, as described by Lord Rayleigh "...somewhat after the manner of a rocket....".

CONCLUSION

The model presented above is limited to analysing the acoustic behaviour of the respiratory system of a ventilated patient. Use of linear systems analysis implies that care must be taken when attempting to make quantitative deductions about gas mechanics in the system, owing to the non-linear nature of gas flow in many practical situations. However, the discussion remains valid over the range of frequencies and tidal volumes encompassed by HFV, and to a certain extent provides a concept that covers the whole clinical range of ventilation. The relationship between the acoustic response of a patient and the gas mechanics (and gas exchange) is not established, but the concept that they are totally independent is unlikely. Practical evidence in bench models, animal models and human subjects suggests that such a relationship exists and may be significant.

Other workers have described four general classes of information required for a complete physiological understanding of HFV (Drazen, Kamm and Slutsky, 1984):

(i) The distribution of airflow within the lung over a wide range of frequencies.
(ii) The basic mechanisms by which local airflows lead to gas transport.
(iii) A model to predict overall gas transport rates.
(iv) An experimental data base which can be compared with model predictions.

To complement this understanding in the clinical situation, a simple model is required which provides optimization criteria that can be realized practically by manipulating ventilator hardware and controls. The development of a valid acoustic model could help to fill this gap if acoustic resonance proves to be significant in promoting gas exchange. In such a case, matching the acoustic output of the ventilator to the acoustic response of a patient could become a clinically useful manoeuvre.

APPENDIX 1

The response of the system in figure 4 is obtained by equating the applied force, $F(t)$, to the sum of (i) the force required to overcome the inertia of the gas in the rigid tube, (ii) the resistive force opposing motion of this gas, and (iii) the force attributable to the compliance of the thoracic volume.

Let x = the axial displacement of any particle of gas in the tube.

ρ = the density of the gas in the tube.

Then the inertial force, F_i, required = mass of gas × acceleration:

$$F_i = L\,.\,S\,.\,\rho\,.\frac{d^2x}{dt^2}$$

The resistive force, F_r, opposing motion of the gas, is proportional to the velocity of flow in the tube. This force may be approximated to the sum of the acoustic radiation resistance of a piston in an infinite baffle (Kinsler and Frey, 1962) and the resistance to flow attributable to the tube, R_f.

$$F_r = \left[\frac{\rho\,.\,a\,.\,k^2\,.\,S^2}{2\pi} + R_f\right].\frac{dx}{dt}$$

where a = velocity of sound, k = wave number = $2\pi/\lambda$.

Further consideration of these resistive factors is presented later.

The force due to the compliance of the enclosed volume, F_c, is given by the product of the increase in pressure resulting from the displacement of the gas in the tube, x, and the cross-sectional area of the tube:

$$F_c = S.x.\frac{1}{C}.S = \frac{S^2}{C}.x$$

Thus the equation representing the response of the system is:

$$F(t) = F_i + F_r + F_c = \left[L.S.\rho\right]\frac{d^2x}{dt^2} + \left[\frac{\rho.a.k^2.S^2}{2\pi} + R_f\right]\frac{dx}{dt} + \frac{S^2}{C}. \qquad \text{(a)}$$

As can be seen, this is a linear second order differential equation characteristic of a simple damped resonant system. It appears more familiar when transformed into a form representing an analagous electrical circuit. Since displaced volume, v, is the acoustic analogue of electrical charge, and rate of volume displacement, dv/dt, is analagous to electrical current, substituting v/S for x in equation (a) gives:

$$\frac{F(t)}{S} = \left[\frac{L.\rho}{S}\right]\frac{d^2v}{dt^2} + \left[\frac{\rho.a.k^2}{2\pi} + \frac{R_f}{S^2}\right]\frac{dv}{dt} + \frac{1}{C}.v \qquad \text{(b)}$$

from which:

$$F(t) = K_i.\frac{d^2v}{dt^2} + K_r.\frac{dv}{dt} + K_c.v \qquad \text{(c)}$$

where K_i, K_r and K_c are coefficients representing inertance, resistance and compliance respectively.

This is similar to the equation representing a simple R, L, C circuit:

$$V = L.\frac{d^2q}{dt^2} + R.\frac{dq}{dt} + \frac{1}{C}.q$$

The resonant frequency for the electrical circuit is given by:

$$f_0 = \frac{1}{2\pi}\sqrt{\frac{1}{L.C}}$$

from which can be seen that a basic resonant frequency can be obtained from equation (b):

$$f_0 = \frac{1}{2\pi}\sqrt{\frac{S}{L.C.\rho}}$$

where L = effective length of the upper airway, S = effective cross-section of the upper airway, ρ = density of gas, C = thoracic compliance.

APPENDIX 2

Acoustic impedance and the conducting airways

The transmission of acoustic waves through the conducting airways will be dependent on the acoustic impedance presented to the waves at any given point within the system. The acoustic impedance is defined by the ratio of acoustic pressure to volume velocity.

In the ideal case of plane waves travelling along an infinite rigid-walled tube, the acoustic impedance seen at any point is constant and dependent on both properties of the medium and the dimensions of the tube (Kinsler and Frey, 1962):

$$\text{Acoustic impedance, } Z = \frac{\rho a}{S}$$

where a = velocity of propagation, ρ = density of gas in the tube, S = cross sectional area of the tube.

In this case the acoustic impedance is known as the characteristic acoustic impedance and is directly analogous to refractive index in the transmission of light. Partial transmission and partial reflection of light occur with changes in refractive index. In a similar way, acoustic waves will undergo partial reflection and transmission at any point where the acoustic impedance changes, such as might occur with changes in the geometry of the tube. In these situations the reflected component will be travelling in the opposite direction to the incident wave. The summation of incident and reflected waves travelling in opposite directions produces the conditions under which standing waves or resonance may be produced.

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MYASTHENIA GRAVIS AND CARDIAC SURGERY

A Case Report

C. APS AND G. O'SULLIVAN

SUMMARY

This paper describes the successful management of a diabetic patient with bulbar myasthenia who underwent mitral valve replacement and coronary revascularization.

Heart disease specific to myasthenia gravis has been described, the lesion most frequently seen being focal areas of myocarditis (Hofstad et al., 1984). However, cardiopulmonary bypass in a patient with myasthenia gravis has not been reported previously. This paper describes the management of a patient with myasthenia gravis who required both coronary revascularization and mitral valve replacement.

CASE REPORT

The patient, a 53-yr-old, 65-kg woman, had suffered from myasthenia gravis for 19 yr and insulin-dependent diabetes mellitus for 26 yr. Ten years previously a thymectomy had been performed because of the progressive deterioration of her myasthenic symptoms—which included both bulbar and skeletal muscle weakness. This was followed by a difficult 3-month period of intensive care which was complicated by poor diabetic control, respiratory failure and two episodes of asystolic cardiac arrest. A temporary tracheotomy was performed during this time to allow weaning from mechanical ventilation. Nine years later the patient had suffered a transient ischaemic attack, affecting her left arm, from which she had recovered fully.

On the present admission the preoperative symptoms included grade 2 effort intolerance limited by dyspnoea and chest pain. There was also some weakness of the bulbar and extra-ocular muscles, mainly occurring in the early morning. Motor power in the limbs was unaffected. Cardiac catheterization demonstrated moderate calcific mitral stenosis with a mean transmitral gradient of 17 mm Hg. Mean pulmonary artery pressure and mean left atrial pressure were 25 mm Hg and 18 mm Hg, respectively. Cardiac output was 4.7 litre min^{-1} (cardiac index 2.7 litre min^{-1} m^{-2}) and pulmonary arteriolar resistance was 1.49 units. Cineangiography showed a normal sized, uniformly contracting left ventricle with an ejection fraction of 0.64. There was a dominant left coronary artery system with 60% stenosis in both the left anterior descending and distal right coronary arteries. Arterial pressure was 190/ 80 mm Hg. ECG showed sinus rhythm and changes indicative of left atrial hypertrophy. Positive chest x-ray findings included upper lobe diversion and left atrial enlargement. Tomography revealed a narrowing of the upper trachea consistent with a previous tracheostomy. Biochemical and haematological tests were unremarkable. At the preoperative examination limb power and swallowing were normal, there was no diplopia or ptosis, but the FVC was 1.5 litre with an FEV_1 of 0.8 litre. Daily oral drug therapy included pyridostigmine 60 mg 12 hourly, neostigmine 60 mg in divided doses and aspirin 75 mg. Diabetic control was achieved with soluble insulin 16 u plus isophane insulin 6 u in the morning, and soluble insulin 6 u plus isophane 10 u in the evening.

Intraoperative management

The patient received no insulin or anticholinesterase therapy on the morning of surgery and

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was premedicated with papaveretum and hyoscine. She was the first patient on the morning operating list. In the anaesthetic room, i.v. and i.a. cannulae were inserted under local anaesthesia. General anaesthesia was induced using midazolam 1.5 mg, fentanyl 100 µg and etomidate 10 mg. Atracurium was administered in 1-mg increments while neuromuscular transmission was assessed at the ulnar nerve using a non-quantifiable peripheral nerve stimulator (Wakeling Instruments Ltd). After the patient had received atracurium 5 mg, and despite an unchanged response to train-of-four stimulation, it was necessary to assist ventilation. Laryngoscopy was performed, the cords sprayed with 4% lignocaine and the trachea intubated without difficulty. The lungs were ventilated with nitrous oxide and 0.5% halothane in oxygen until cardiopulmonary bypass was instituted. Neuromuscular function was monitored at 30-min intervals using train-of-four and tetanic stimulation of the facial nerves. Insulin (Actrapid) was infused by syringe pump at a rate determined by a sliding scale regimen against 1-hourly BM-stix estimations. As the patient was allergic to penicillin, erythromycin was administered as antibiotic prophylaxis; this did not affect the train-of-four or post-tetanic responses. A further atracurium 2 mg was given empirically at the institution of cardiopulmonary bypass. The bypass technique included haemodilution, cardioplegic arrest and moderate whole body hypothermia (28 °C). The pump priming volume was Hartmann's solution 2 litre and flow was calculated on the basis of 2.4 litre/m^2 body surface area. A mechanical (Duromedics) mitral valve prosthesis was inserted and two saphenous vein aortocoronary bypass grafts were anastomosed without difficulty. There were no diaphragmatic or other muscle movements despite, first, the hypercarbic conditions associated with cardiopulmonary bypass and, second, the fact that no fade or post-tetanic facilitation were observed throughout the whole procedure. During rewarming, fentanyl 100 µg, alfentanil 1 mg and midazolam 1.5 mg were given i.v. and an infusion of glyceryl trinitrate commenced. Weaning from bypass was achieved without inotropic support, and the patient remained in sinus rhythm with low venous and pulmonary arterial pressures. Vasodilator therapy was continued in order to enhance peripheral perfusion, together with frusemide 20 mg and a low-dose infusion of dopamine to maintain urine output. Following bypass no volatile agents were administered and sleep was maintained with nitrous oxide–oxygen and increments of fentanyl.

Postoperative management

The patient was transferred to the Intensive Care Unit for elective overnight ventilation. An infusion of morphine was used to provide sedation and analgesia. On the morning following surgery, the patient was awake and alert, the chest x-ray was clear, the arterial blood-gas tensions were normal and all cardiovascular indices were stable. The surgical drains were removed, following which the morphine infusion was discontinued. The forced vital capacity, measured with a Wright's respirometer, was 1 litre. A "Tensilon" test was performed using edrophonium 10 mg with glycopyrrolate 0.3 mg i.v., subsequent to which the FVC was 1.2 litre. Neostigmine 1.25 mg and glycopyrrolate 0.25 mg were administered i.v., following which the tracheal tube was removed. One hour after extubation the FVC was 1.1 litre, the pattern of ventilation was satisfactory, the respiratory rate was 18 b.p.m. and blood-gas tensions were normal.

Thirty minutes later the patient suddenly became distressed and was unable to cough, her arterial pressure increased and she developed multifocal ventricular ectopics. Edrophonium i.v. did not improve her condition and the trachea was reintubated rapidly following the administration of midazolam 12.5 mg i.v.. The morphine infusion was reintroduced.

After a further 24 h the patient again fulfilled the criteria for attempted extubation. Following edrophonium 10 mg and glycopyrrolate 0.3 mg i.v., the FVC was in excess of 1 litre and the trachea was extubated for the second time. A reduced amount of her normal oral anticholinesterase therapy was administered via the nasogastric tube and glycopyrrolate was given i.m. on a regular basis in order to minimize secretions. FVC and blood-gas analyses were performed at 1-hourly intervals. The morphine infusion was continued on this occasion and the rate adjusted to ensure normocarbia. One hour after extubation, inspiratory stridor developed. This was managed by the administration of a helium–air–oxygen mixture via an MC mask, together with dexamethasone i.m. The stridor resolved completely over the next 2 h.

The patient was discharged to the general ward on the 3rd day after operation, by which time she was re-established on her normal maintenance regimen of oral anticholinesterase therapy. FVC remained just over 1 litre on repeated measurements, with an FEV_1 of around 0.8 litre. Radiological evidence of right basal lung collapse resolved with physiotherapy, and there was no difficulty with diabetic control. Progress was marred by a visual defect which was demonstrated, by computerized axial tomography, to be the result of a small parieto–occipital infarct, presumed to have occurred during the operation. She was discharged from hospital after 1 month.

DISCUSSION

There have been many suggestions as to how the myasthenic patient should be managed following major surgery (Foldes and McNall, 1962; Loach, Young and Spalding, 1975), but there have been no previous reports of the management of such patients undergoing cardiac surgery. Anaesthesia for myasthenic patients requiring open heart surgery differs in some important respects from that used in non-cardiac operations. First, deep inhalation anaesthesia sufficient to prevent movement is hazardous in cardiac disease, and inappropriate following bypass. Second, in order to avoid muscle movement and, in particular, diaphragmatic movement, during the period on bypass a degree of neuromuscular blockade is required. For these reasons anticholinesterase therapy was withdrawn on the day of operation and neuromuscular blockade was provided using atracurium. The known advantage of atracurium over other agents in this context is its non-enzymatic (Hofmann) degradation to non-active metabolic products (Hughes and Chapple, 1981)—the degradation being delayed under the conditions peculiar to extracorporeal circulation (Flynn, Hughes and Walton, 1983). In addition, this agent has previously been used successfully to provide neuromuscular blockade in myasthenic patients undergoing thymectomy or abdominal surgery (Baraka and Dajani, 1984; Ward and Wright, 1984). From these reports, the required dose of atracurium appears to be greater in patients maintained on anticholinesterase therapy than in those in whom it was withdrawn on the day of operation. In the latter circumstance, initial dose requirements were observed to be around 0.1 mg kg^{-1}, which compares well with the intubation dose in this patient of 0.077 mg kg^{-1}.

Sleep was maintained throughout the procedure by a regimen similar to that normally utilized in non-myasthenic cardiac surgical patients. Because there was little evidence of skeletal muscle paralysis, it is presumed that both the anaesthesia and hypothermic conditions during bypass contributed to the lack of movement.

Multivariate discriminate analysis has been applied to the preoperative physical, historical and laboratory data of myasthenic patients requiring thymectomy in an attempt to predict the need for postoperative ventilation (Leventhal, Orkin and Hirsh, 1980). It was found that the main risk factors were the duration of myasthenia, the presence of respiratory disease, the daily dose of pyridostigmine and vital capacity. Using these four factors, a preoperative scoring system was used to predict correctly the need for postoperative ventilatory support in 91% of patients undergoing thymectomy. The patient presented here required a longer than usual period of ventilation following coronary revascularization and mitral valve replacement which, according to the scoring system, was predictable solely in terms of her limited vital capacity and duration of myasthenia.

In an attempt to avoid the morbidity associated with prolonged postoperative artificial ventilation, a fairly aggressive attempt was made to re-establish spontaneous ventilation, coughing, mobilization and physiotherapy. The decision to reintubate on the 1st day after operation, when the patient became distressed, did not deter a second attempt 24 h later. The stridor that subsequently developed was assumed to have occurred as a consequence of her previous tracheostomy, and was managed conservatively in order to avoid further tracheal trauma associated with re-intubation.

The parieto–occipital infarction produced a visual field defect but did not impair other functions. Such complications mar an otherwise successful operative outcome. Unfortunately, neurological deficits are not uncommon following coronary artery surgery and, of these, ophthalmological abnormalities have been observed to account for 25% of the complications that do occur (Shaw et al., 1985).

In conclusion, a patient with myasthenia gravis who required cardiac surgery was successfully managed by the careful combination of anaesthetic techniques that are required both in myasthenia gravis *per se* and for open heart surgery.

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BOOK REVIEWS

Year-Book of Anaesthesia 1985. Edited by R. D. Miller. Published by Year Book Medical Publishers, Inc., Chicago. Pp. 395; indexed; illustrated. Price £41.00.

The 1985 *Year-Book of Anaesthesia* is number 36 in the series. It is edited by Professor Ronald D. Miller, M.D., with the assistance of four associate editors, all of whom are American Professors of Anesthesiology.

The book contains abstracts from 299 articles taken from 72 journals which are mainly of American and European origin. The layout of the book is excellent. It has 13 chapters which cover a very broad range of topics of interest to anaesthetists, thus ensuring that the book will have wide appeal. A Table of Contents at the front of the book lists the chapters, many of which are split into sections which enables the reader to pick out abstracts pertaining to a particular topic. The abstracts themselves are also very clearly laid out with the title, authors names and source easily identifiable. The abstracts are of sufficient length to be meaningful and many are illustrated with figures and legends which ensure their clarity. The majority of the abstracts are followed by editorial comments which vary greatly in length and content. Some comments offer constructive criticism of the articles reviewed, others provide interesting anecdotes regarding the editor's own practices and views. In my opinion the most useful are those which cite other papers and review articles pertaining to the topic under discussion. The book concludes with a comprehensive subject and author index.

This book culls a great deal of new information covering many topics of interest, and also provides the reader with pointers for further study. Thus, whether clinicians are engaged in serious study of the literature or in light reading of current trends, I imagine that they will find the book stimulating. However, as it carries a fairly high price tag for any individual I would recommend that Departmental Libraries start a collection of *Year Books* with this one if they haven't already done so.

S. M. MacVicar

Lectures in Anaesthesiology, 1985/2. Edited by John S. M. Zorab and R. M. Weller. Published by Blackwell Scientific Publications. Pp. 131. Price £8.50.

This book, which is published on behalf of the World Federation of Societies of Anaesthetists (WFSA), consists of eight chapters on unrelated subjects.

Dr John Nunn's chapter on Pulmonary Problems in Anaesthesia is based on a lecture delivered at the World Congress of the WFSA in Manila in 1984. It is a concise summary of current thinking about how respiratory parameters are affected by anaesthesia and by controlled ventilation.

Professor Harrison, of Capetown, writes on Deaths Attributable to Anaesthesia. He reviews many past surveys on Mortality and Morbidity, discussing their shortcomings and the inherent difficulties in analysing their data. If the figures and tables, which are not well explained and sometimes irrelevant, can be disregarded, the actual script is factual and informative.

The chapter by Dr Allison Holloway, of Brisbane, is on Carbon Dioxide Absorption in Anaesthesia. It is a model of good writing, easy to read, and packed with historical, scientific and clinical information of interest to every anaesthetist—and especially to those studying for higher qualification. This is a particularly good chapter which provides stimulating reading.

Dr Douglas Howat's chapter is full of sensible advice from an expert with a vast experience of Anaesthesia for Biliary and Pancreatic surgery. This is an orderly and comprehensive presentation which includes much of the medical and surgical background to the subject which is essential to its understanding. The inclusion of a detailed description of the author's technique, evolved over many years, of high extradural blockade is particularly interesting, containing as it does many practical tips, together with good and proven reasons for not opting for some of the variations in the technique.

Professor John Norman's chapter provides a neat and succinct account of the Oxygen Transport Diagram. The Diagram is then used to base a clear and scientific explanation of the physiological mechanisms which enable patients to compensate for altered transport. This is indeed, as he himself states, "a useful *aide-memoire*", and it will be of great interest to all who like to link science with practice.

There is a more esoteric chapter on Energy Supply and Expenditure in Critically Ill Patients, written by Professor Jurgen Kilian, of Ulm. This is a concise account of a difficult subject, and although all the figures would have benefited from greater explanation either in the script or in the legends, the metabolic and biochemical needs of the ill patient are well presented, and this is used as a starting-point on which to explain how a parenteral nutrition regimen may be devised.

The remaining two chapters concern anaesthesia for children. The first by Dr John Lunn is a personal account of the author's practice. Many anaesthetists may disagree with his views, in particular his reluctance to allow a child to choose between an intravenous or inhalation induction. Nevertheless, there are some valuable points of technique.

The final chapter by Professor David Steward of Vancouver, is also on Paediatric Anaesthesia, and is reprinted from 1984 *Advances in Anaesthesia* Vol. 1. It is a comprehensive and authoritative review of the subject, beginning with a well-balanced section on relevant psychology and anatomy, then drugs, equipment, techniques and management, and finally postoperative care, monitoring and analgesia. This is a well-written chapter and is effectively a mini-textbook for mini-patients.

These lectures represent good value at £8.50 per volume. The good chapters are very good indeed and all the others have much to offer. All anaesthetic department libraries should subscribe to this lecture-series, and it will be particularly helpful for those for whom it was designed—clinicians who have no easy access to lectures or meetings.

A. G. Macdonald

Lectures in Anaesthesiology, 1986/1. Edited by J. S. M. Zorab and R. M. Weller. Published by Blackwell Scientific Publications. Pp. 98; illustrated. Price £8.50.

This volume of the *Lectures in Anaesthesiology* series of two volumes or issues a year contains monographs on the following six topics: the pharmacology and toxicity of local anaesthetics; the effects of anaesthesia on uteroplacental blood flow; asthma and the anaesthetist; postoperative pain relief, the anaesthetic implications of porphyria; and the analgesic effects of intrathecal and extradural opioids. A brief historical note on the development of anaesthesia in the prone position for chest surgery is also included.

As with previous volumes in this series, the major irritation to the reader is the lack of consistency of style. For instance, a chapter from a contributor from the U.S.A. will use American spelling, but the non-American authors tend to use English spelling. The chapters in themselves are informative and interesting. However, it really is quite annoying for authors repeatedly to mention that an important paper exists, only for the reader to find that the citation doesn't appear in the list of references. Some contributors give no references at all but, instead, offer a list of "further reading", which is sometimes very sparse indeed.

Some reviewers of previous volumes in this series have suggested that the material is really only for anaesthetists in the developing countries. This is patently nonsense and all the material offered is generally very clearly presented and is to quite a high standard. I would strongly recommend most of it to the examination candidate; just to take a single example, the article on the pharmacology and toxicity of local anaesthetics in this volume is succinctly and concisely written by a master and can hardly be bettered by the chapters on the same subject which appear in the various standard textbooks on anaesthesia. However, some contributions can hardly be called "lectures", but have been considerably worked up into concise and sometimes complex monographs.

This reviewer likes the series, for it deserves widespread success for its aims in the educational field. The editors obviously have a difficult job—so do all editors—but they must get their act together and do some firmer editing to prevent this series from just being a collection of highly individual disparate papers, albeit by highly respected experts, which are thrown together in sufficient numbers to make up an issue.

A. P. Adams

Emergencies in Clinical Medicine. Edited by H. J. Kennedy. Published by Blackwell Scientific Publications. Pp. 487; indexed; illustrated. Price £18.50.

Clinicians continually require new information to adapt their practices to provide "state-of-the-art" patient management. A popular way to acquire this information, it seems, is the modest-sized volume of collected reviews, recent advances or updates. In the present work, Dr Kennedy has assembled a number of distinguished contributors who provide chapters on all the common medical emergencies likely to be found in a general hospital. The book is not targeted at beginners, but is designed to be "an aid to physicians who already have a knowledge of practical management of medical emergencies". The subjects covered are wide-ranging and include useful chapters on the epidemiology of medical emergencies and their presenting symptoms as well as on specific aetio-pathological entities.

In the introduction Dr Kennedy indicates that the individual authors were asked, not only to give practical guidance on management, but to discuss current limitations in knowledge, current controversies, and to give their reasons for following particular approaches to management. In their response to this injunction the individual authors have varied rather widely.

For an established clinician to integrate to his practice a new development requires, ideally, information from new, well conducted original studies relevant to the question in hand. Such studies will appear in the literature as original articles and the practical value of a review is to place such new developments in context and to provide adequate bibliographies. Many of Dr Kennedy's authors have indeed taken this approach, and those of us who may have missed items in the original literature can readily pick up the references. However, some chapters are thoroughly unsatisfactory, consisting of an account of the clinical condition with references only to standard text books, an approach which provokes the view that it would be simpler to read the text book in the first place.

Review articles frequently irritate the reader with recommendations that such and such a form of treatment "may be valuable", or this or that manoeuvre "has been tried". To a clinician seeking practical guidance, such observations are worse than useless and this volume sadly is not free from such frustrating enjoinders. However, not all chapters can so be criticized, as many give clear operational definitions of the clinical entities with clear recommendations for treatment often laid out graphically as decision trees or algorithms.

A work such as this, seeking to bridge the gap between text books of medicine and the original literature, is likely to meet with most success with beginners in the subject who are avid for practical guidance. For more experienced clinicians the success of the work in reaching its audience may, in a curious way, be inversely proportional to the need, for surely as we extend our experience we tend to become more fixed in our clinical practices and find it easier to regard a fresh account as merely a catalogue of someone else's prejudices. To overcome such attitudes, a work such as this has to convince the reader that there is genuinely something new to be learned and this volume does so in some of its chapters. The book, at 487 pages, makes considerable demands on time and I cannot imagine wishing to read it all when the competing literature is so vast. Whether the demand on the pocket can be met will depend, as usual, on the size of the pocket.

W. G. Anderson

Anaesthesia for Ambulatory Surgery. Edited by B. V. Wetchler. Published (1985) by J. B. Lippencott Company, Philadelphia. Pp. 476; indexed; illustrated.

A most welcome and timely addition to the anaesthetists bookshelf, this book sets a high standard Ambulatory anaesthesia is not synonymous with outpatient anaesthesia, but the difference is, in the U.K., largely one of semantics, as they both have similar objectives. The principal difficulty in actively promoting ambulatory surgery is the reconciliation of the apparent paradox of the provision of acceptable facilities, the selection, preoperative investigation and equally safe treatment of patients with that available in hospitals, which cost so much more to equip and operate. This book is the product of the extensive experience and the enthusiasm of a number of authorities who critically analyse their experiences and present the solution clearly and most persuasively. Success is attained by the rigorous and unyielding application of high standards: costs can be reduced without compromising patient safety.

The increasing popularity of this type of unit, often apparently freestanding in the U.S.A., depends on strict attention to detail in its planning, the careful selection of staff and their continuous education. The importance of the design and integrated function is comprehensively discussed in the first part of the book. this is perhaps less relevant in the U.K., where the majority of out patient surgical facilities are integrated with hospitals, but the principles of care presented so clearly are very relevant.

Obviously, this is a book aimed at the American anaesthetist, but it is not parochial, and the U.K. literature is referred to when appropriate. One distinct difference is that the ambulatory unit is responsible for the provision of after care, and patients are followed up by telephone and postcard. In the U.K., community services provide the convalescent care.

Suitable anaesthetic techniques are considered in great detail with appropriate and comprehensive references. The emphasis is always on patient care and safety. The references are worthy of comment: their presentation is, in my experience, unique. At the end of each chapter, the references are placed in alphabetical order, and numbered in that order. References in the text are given the appropriate number. This produces a neat and economical solution to a minor but irritating problem and should be widely copied.

The editor is to be congratulated in producing such a book, the contributors' enthusiasm is evident, but the evidence relating to ambulatory anaesthesia is carefully and critically examined. Clear and sensible guidance is given, some "real life" situations are presented in the form of question and answer; the issues are not fudged. Copies of leaflets successfully used in large units, which cover all relevant aspects of care and which are given to ambulatory surgical patients, are usefully included.

The volume is well produced, with clear illustrations. Although quite expensive, it is a bargain; no comparable book exists. It should be compulsory reading for anyone involved in outpatient anaesthesia, and is interesting and informative to those who are not.

J. Thorburn

Obstetric Anaesthesia and Analgesia, 3rd Edn. By D. D. Moir and J. Thorburn. Published by Ballière-Tindall. Pp. 390; indexed. Price £17.95.

The first two editions of this book, published in 1976 and 1980, were considered essential reading for obstetric anaesthetists and those preparing for postgraduate examinations in anaesthesia. The present volume has been extensively revised, the sections on gastric acidity, failed or difficult intubation, extradural anaesthesia for Caesarean Section and the use of spinal anaesthesia having been rewritten. Dr Moir has been joined in authorship by his colleague, Dr Thorburn, and it is evident throughout that both are strong advocates for the greater use of regional anaesthesia.

The first three chapters deal with the history of obstetric anaesthesia, the physiology of pregnancy and labour and the pharmacology of drugs used in labour. It is my view that the marked physiological changes occurring during childbirth and their influence on pharmacokinetics merited more detailed consideration. Nevertheless, these chapters contain a wealth of material, together with references to recent work, and the reader can easily pursue a particular topic. The inadequacies and dangers of the currently available drugs used for systemic analgesia are documented, yet one must remember that they still remain the mainstay of obstetric analgesic practice in the United Kingdom.

The section on general anaesthesia recommends one method for all situations. I would have liked to see a diagram or photograph showing the correct method of applying cricoid pressure. The doses of thiopentone sodium 3–3.5 mg kg^{-1} and etomidate 0.3 mg kg^{-1} are, in my opinion, too small to maintain unconsciousness in all patients during intubation and, indeed, may allow active movement if this procedure proves difficult. The question of hypo- and hyperventilation is considered in detail, and I would have liked a firm recommendation for end-tidal carbon dioxide monitoring in all patients. This would also help in ready recognition of inadvertent oesophageal intubation. The basic concepts relating to the management of general anaesthesia in obstetric patients are excellent.

Dr Moir has done much to popularize extradural analgesia and to establish its safe practise in British obstetrics. It is evident from the section on regional anaesthesia that he recognizes the problems associated with its use in the non-teaching and smaller obstetric unit. The techniques, the institution of the block, its management and uses are covered in detail. However, is the extradural space a mean or average 7 cm from the skin in the lumbar region? When dealing with extradural anaesthesia for Caesarean Section it is suggested that, if the blockade is inadequate after a substantial dose of bupivacaine, further spread might be obtained by additional lignocaine and this may be safer than bupivacaine. This could be dangerous, as the toxic effects of local anaesthetics are additive and the reviewer feels that this advice in no way diminishes the risk of overdosage reactions. Spinal anaesthesia, which is becoming more popular, is well described. However, manufactured introducers for 25-s.w.g. spinal needles are readily available, so there is no need to make-do with the "make-shift" needle suggested. Infiltration of the skin and interspinous ligaments is not considered an essential part of the author's technique, yet if a second attempt (not uncommon) has to be made, the patient's co-operation may be lost because of the pain from a lack of analgesia.

The management of maternal and infant complications of labour are discussed, together with sections on paracervical and pudendal block anaesthesia. The section on pre-eclampsia underlines the need for intensive management. In correcting acidosis in the newborn, a 4.2% solution of sodium bicarbonate is less irritant than the recommended 8.4%. The book also contains a chapter on the management of pregnancy and labour by an obstetrician (M. R. Whittle), so the reader is given a good overall view of the problems likely to present in the delivery room.

This book is well produced, written in a clear distinctive style and every chapter has an extensive up-to-date bibliography. It is strongly biased towards regional anaesthesia and only time will tell if this will reduce maternal mortality associated with anaesthesia. Like previous editions, it is essential reading for all associated with obstetric analgesic and anaesthetic practice.

J. Moore

Guidelines in Clinical Anaesthesia. By P. Hutton and G. Cooper. Published by Blackwell Scientific Publications. Pp. 403, indexed; illustrated.

The time honoured advice of the physician who does not understand his role in preoperative assessment is "avoid hypotension, hypoxia and hypercarbia". This book goes one step further. In the section on cerebrovascular disease, it states "The patient should be maintained normotensive by application of the techniques described in Chapter 1". Would that anaesthesia were that simple! My main criticism of this book is that it frequently offers a simplistic approach to problems posed by patients who, in real life, do not conform to any norm.

The authors' objective is to present a revision of the theoretical aspects of medical problems with advice on preoperative assessment and the presentation of guidelines to intraoperative and postoperative anaesthetic management. These objectives are achieved in Chapter 1, which is devoted to cardiovascular disease. It contains useful information in a clear format—a chapter that all examinees should read. At the end of the book are chapters on Psychiatry and Anaesthesia and Old Age, where the educational approach, based on general principles has much to commend it. The middle of the book, however, tends to become a seemingly endless list of what to do in various conditions. It will undoubtedly be used as a reference text, but makes for very heavy reading.

When the authors have dealt with general principles and outline an approach to a problem, I found the advice to be refreshingly down to earth. However, when specific management is offered, it is inevitable that there is bound to be disagreement and I would take issue with much of the practical advice offered. To give just one example, the authors state that tachycardia should be avoided when antagonizing neuromuscular blockade in patients with mitral stenosis, but their suggestion to trainees that an alternative approach is to use atracurium or vecuronium and allow it to wear off spontaneously is, without qualification, not appropriate advice. In some parts of the text, the authors appear to lose their way, straying into intensive care, which of necessity must be dealt with very superficially.

The text is 385 pages long, and references are not provided in the text, which is an advantage. At the end of each chapter, a list of articles and chapters for further reading are provided.

This book will undoubtedly find its way into personal collections of junior anaesthetists; it will be used as a day-to-day reference book when confronted with specific problems. I would urge them not to follow the advice proffered without careful consideration of the specific problems that their patients present. As an educational text with examinations in mind, I would recommend this book to anaesthetic trainees.

P. Barnes

Neonatal Anaesthesia and Perioperative Care, 2nd Edn. *Current Topics in Anaesthesia*, series 5. By David J. Hatch and Edward Sumner. Published (1986) by Edward Arnold, London. Pp. 271; illustrated; indexed. Price £33.00.

Neonatal Anaesthesia in the *Current Topics in Anaesthesia* series first appeared in 1981. The authors have now revised and updated the contents and have wisely decided to enlarge the original remit to include perioperative care. This is because there have been considerable advances in the art and science of neonatology, with resultant increase in survival of many preterm babies who, hitherto, would not have been even considered viable let alone present for anaesthesia and surgery. Their successful outcome is, therefore, vitally dependent on meticulous pre- and postoperative care.

The basic format of the first edition has been maintained, but with considerable expansion so as to incorporate the increased information on drugs, techniques and concepts. The book is divided into sections on perinatal physiology, the surgical neonate (which includes the preoperative preparation), anaesthesia—basic principles, anaesthesia for specific conditions, postoperative care and resuscitation of the newborn. Three appendices cover unusual conditions in the neonate with implications for the anaesthetist, guidelines for drug dosage and normal physiological values in the neonate and adult.

The previous reviewer commended the authors on the clarity, relevance and presentation of their approach to this large subject, and these qualities are much in evidence in the new edition. The text is written with great authority, experience and expertise which has been gleaned from the wealth of clinical work to which the authors are dedicated. More than 500 anaesthetics are administered annually to neonatal patients for all types of surgery at the Hospital for Sick Children, Great Ormond Street, London. Other centres might naturally disagree with certain details of the management described, but as the previous reviewer stated "this reflects a variation in an area where there is art as well as skill".

The quality of production is extremely good and the illustrations clear and concise. Whilst disappointment had been expressed previously about the quality of reproduction of x-ray plates, this aspect is often outside the control of the authors and publishers, and is dependent on the quality of the original x-ray film, which may have been taken under adverse conditions. Care should be taken at the next reprinting or edition to correct the position of fig. 4.22 on page 185, which depicts a barium swallow showing a double aortic arch, in a baby who is apparently being held upside down! Apart from this unconventional illustration, the reader did not detect any other error and the proof reading has been of a very high standard.

This book is clearly to be highly recommended to all those anaesthetists who wish to learn more about the difficulties and dangers of anaesthesia in the newborn, and their successful management.

Gordon H. Bush

The Management of Postoperative Pain. Current Topics in Anaesthesia, No. 8. By Margaret E. Dodson. Published by Edward Arnold, London. Pp. 274; illustrated; indexed. Price £27.50.

It has become a cliché that postoperative pain is badly managed. Fifteen years ago it was also a neglected area of endeavour, but that is not true now. There is hardly an academic department in Britain that does not have a research stake in the subject although, sadly, this intense interest has not led to the breakthrough that will bring painless surgery.

This book is the first to be directed exclusively at the subject of postoperative pain—there being, of course, an abundance of books on general or other special aspects of pain. It offers a thorough review of its subject to a consistent standard, the latter being attributable, I believe, to the fact that this is a single author work apart from two chapters (The Pharmacology of Analgesic Drugs by Dr Barbara Pleuvry and Analgesia in Children by Drs Booker and Nightingale). I recommend the book strongly to both trainee and established practitioner for its clean style and rich store of reference to the far-flung publications on postoperative pain.

The potential weakness of the work is the author's apparent reluctance to call a spade a spade. It is surely not in doubt, for example, that the various regimens for attempting to achieve something approaching either a pharmacokinetic or pharmacodynamic steady state for i.v. analgesics (timed bolus, continuous infusion and patient controlled analgesia) do not work reliably beyond the sphere of the researcher. There is quite enough known about these methods to make it a good betting probability that they are not the answer to the problem, at least in the conventional ward setting. Yet the chapter on these matters, finishing with a list of suppliers of PCA systems, ventures no further than:

> "As a research tool PCA is valuable..."
> "More studies need to be done to clarify..."
> "Even if it should never become...widely used...PCA..."

Equally, in respect of spinal opiates, Dr Dodson leaves the reader with the impression that further evaluation might pull a rabbit from the hat. Is it not more accurate to say that the spinal opiate approach is also limited, if not a blind alley?

The final chapter ("The Way Forward") points in no particular direction. May I offer these thoughts? Suppose we had a long-acting local anaesthetic and a short-acting inhalation agent, both with minimal toxicity and side effects. Would that help?

Alastair A. Spence

Effects of Anesthesia. Clinical Physiology Series. Edited by B. G. Covino, H. A. Fozzard, K. Rehder and G. Strichartz. Published by the American Physiological Society. Pp. 224; indexed; illustrated. Price $44.

The concept of bringing together in one volume the molecular, cellular and whole organism effects of anaesthesia is laudable. There have been a number of advances in these fields which have not yet reached the textbooks and this volume from the American Physiological Society is timely. In order to be intelligible to the non-specialist reader, it is essential that new techniques are explained in sufficient detail to permit understanding of experimental results. Regrettably, this is not the case with the early chapters of the first section on molecular and membrane effects, particularly that by Smith and Butler on nuclear magnetic resonance studies of membranes. The first section is completed by three chapters on local anaesthetic effects on membranes.

In contrast, the opening chapter in the section on the respiratory system by Hornbein is a model of lucidity. The following chapters on the mechanics of respiration, chest wall movement and the pulmonary circulation should be compulsory reading for examination candidates.

The final section on cardiac and circulatory effects includes chapters on i.v. anaesthetic agents and narcotic analgesics and, finally, regional analgesia by the principal editor.

The book is well illustrated and referenced and contains very few errors. The most notable is an error in Equation 1 on p. 125. This book should find a place on the shelves of department libraries as a useful review of current theories, and as a pointer to future research.

C. D. Hanning

Clinics in Anaesthesiology. Volume 3, No. 2: *Neuromuscular Blockade.* Edited by J. Norman. Published by W. B. Saunders Company. Pp. 485; indexed; illustrated. Price £13.75.

This book, one of a series of *Clinics in Anaesthesiology*, is a most useful monograph for anaesthetists, all of whom must need an updated account on neuromuscular blocking agents when the developments in this field are so extensive. It is compact, easily portable and contains, in addition to the exhaustive factual content for its size, the extra asset of impressively comprehensive lists of reference at the end of each chapter. The international list of contributors, from Saudi Arabia to San Francisco and from Groningen to Glasgow, is made up of well known clinicians working in this field, and a high standard is set.

The book initially summarizes the present knowledge of the physiology and pharmacology of the neuromuscular junction, including the drug interactions that occur at this site. This is a most stimulating start useful, not only for examination candidates, but also for more senior anaesthetists wishing to update their knowledge. The theoretical concepts of pharmacokinetics with respect to neuromuscular blocking drugs are then covered, and perhaps it would have been preferable to follow on here with the pharmacokinetics of the anticholinesterases, but for some reason the problems encountered when muscle relaxants are used in patients with hepatic or renal disease are covered first. In these areas marked benefits in patient management have been experienced with the advent of atracurium and vecuronium, and both these topics are detailed well.

Then the lighter reading starts under the heading of "Clinical Practice", with descriptions of the two newer non-depolarizing relaxants atracurium and vecuronium, together with interesting information about the very long acting blocker not yet available in Great Britain—pipecurium. No monograph about neuromuscular blockade would be complete without a chapter on that unique drug, suxamethonium, and it is comprehensively covered, although it is perhaps surprising that it was not the first drug to open this section. An attempt is then made, in two chapters, to contrast the use of muscle relaxants in the U.S.A. and Great Britain. These chapters probably add little to the book and one chapter on the history of neuromuscular blocking agents may have been more informative.

Reviews then follow on three subspecialty areas in which detailed information for clinicians on the use of neuromuscular blockers is less readily available: in children, in the elderly and in ophthalmic surgery. These sections are particularly useful for the anaesthetist who is not regularly working in these fields as they summarize well the present situation. The book ends with two chapters on the monitoring of neuromuscular function—techniques which clinicians are using more and more regularly, and necessarily so, for the rapid recovery from the newer agents may otherwise cause embarrassment for the more junior anaesthetist when rousing exclamations from the surgeon are heard! A chapter on the use of myoneural blockade in patients with muscle disorders, and in particular malignant hyperpyrexia, would perhaps have been preferable, but this is "icing on the cake". This is a useful book and, as it costs only £13.75p, no anaesthetist can afford to be without it.

J. M. Hunter

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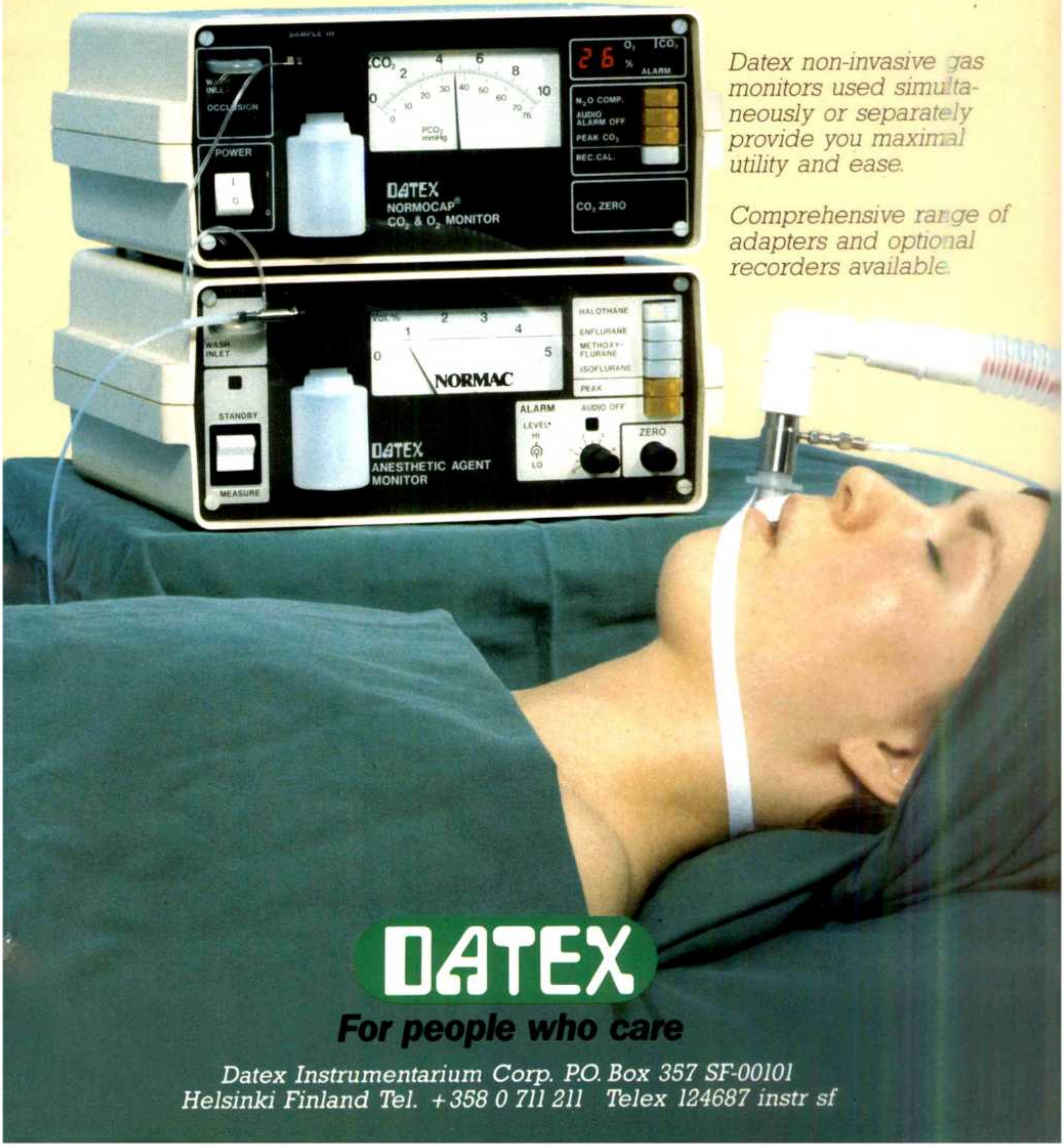

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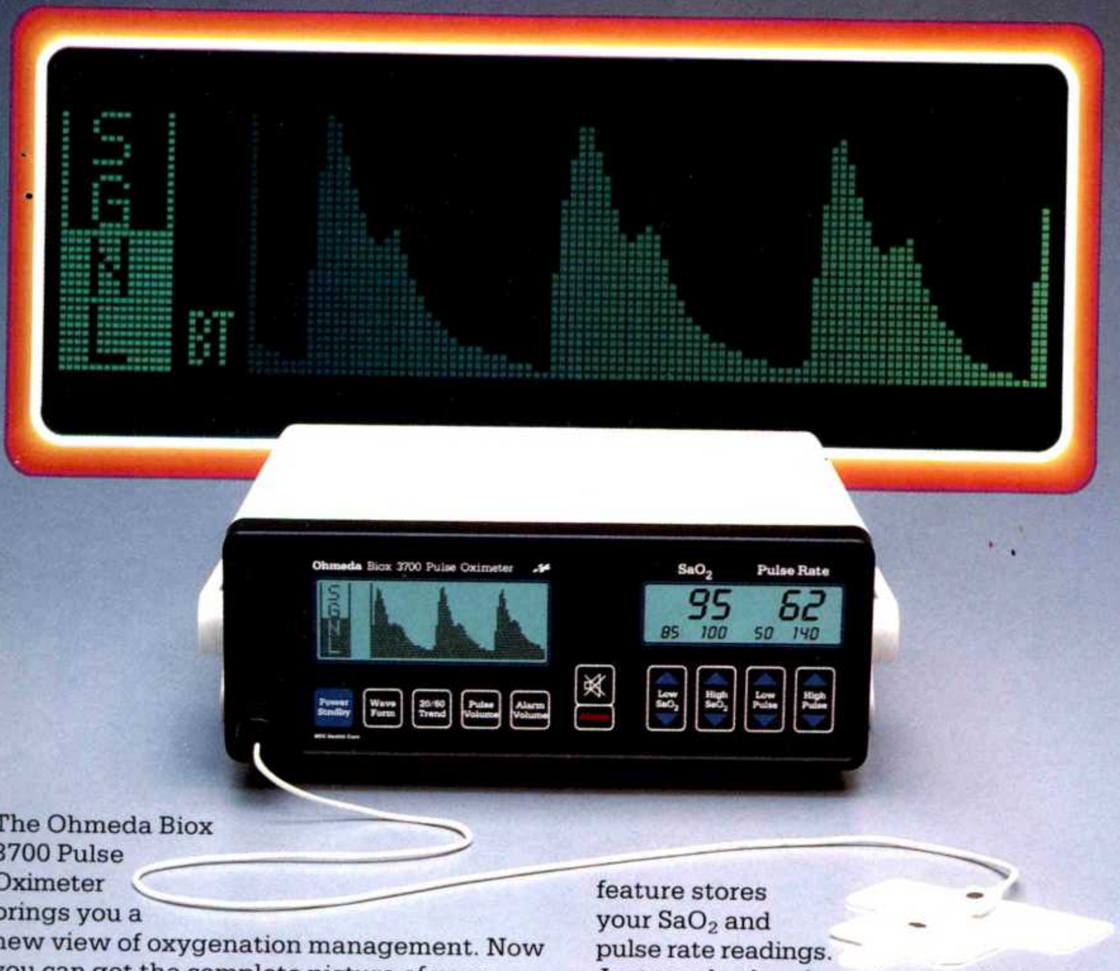

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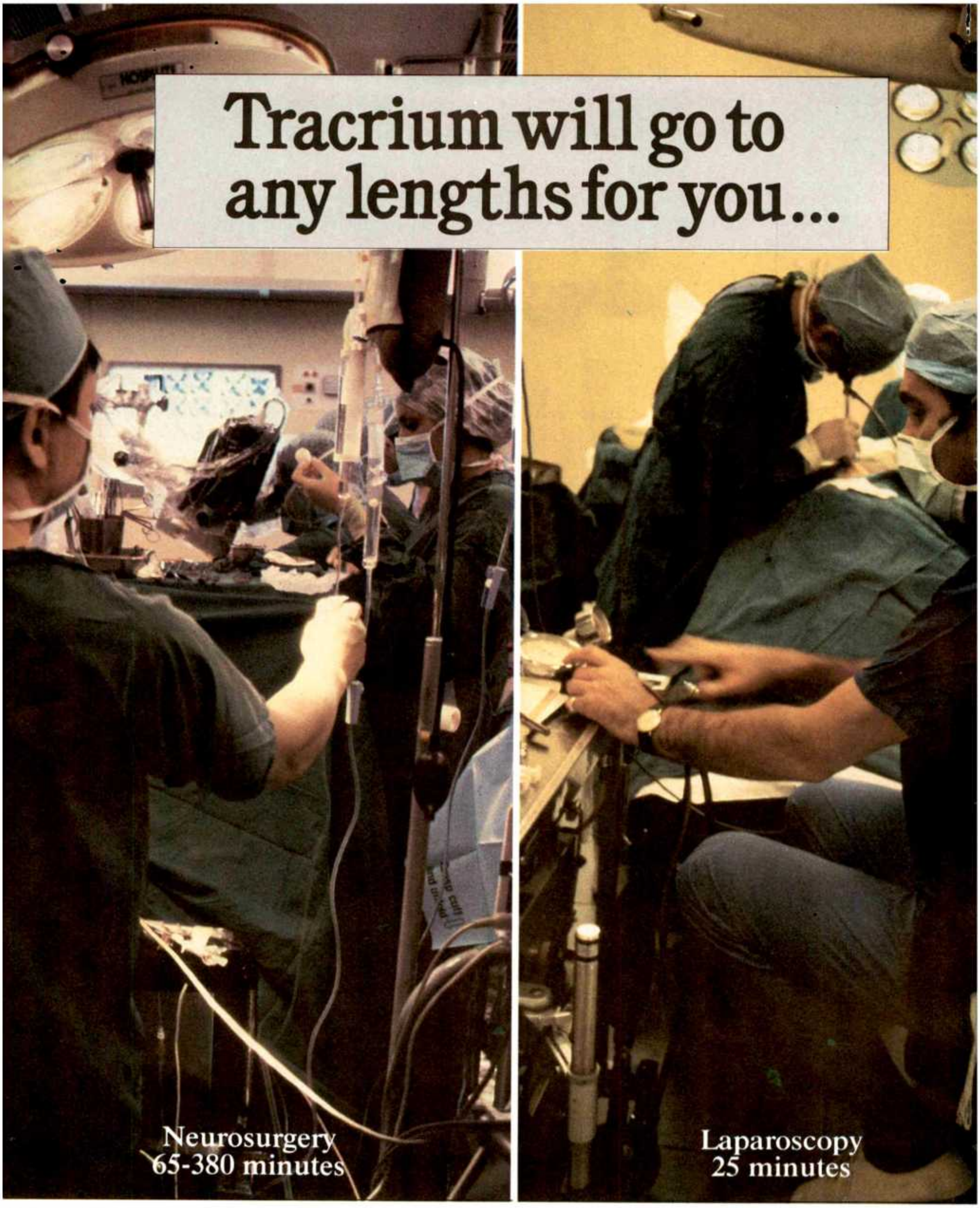

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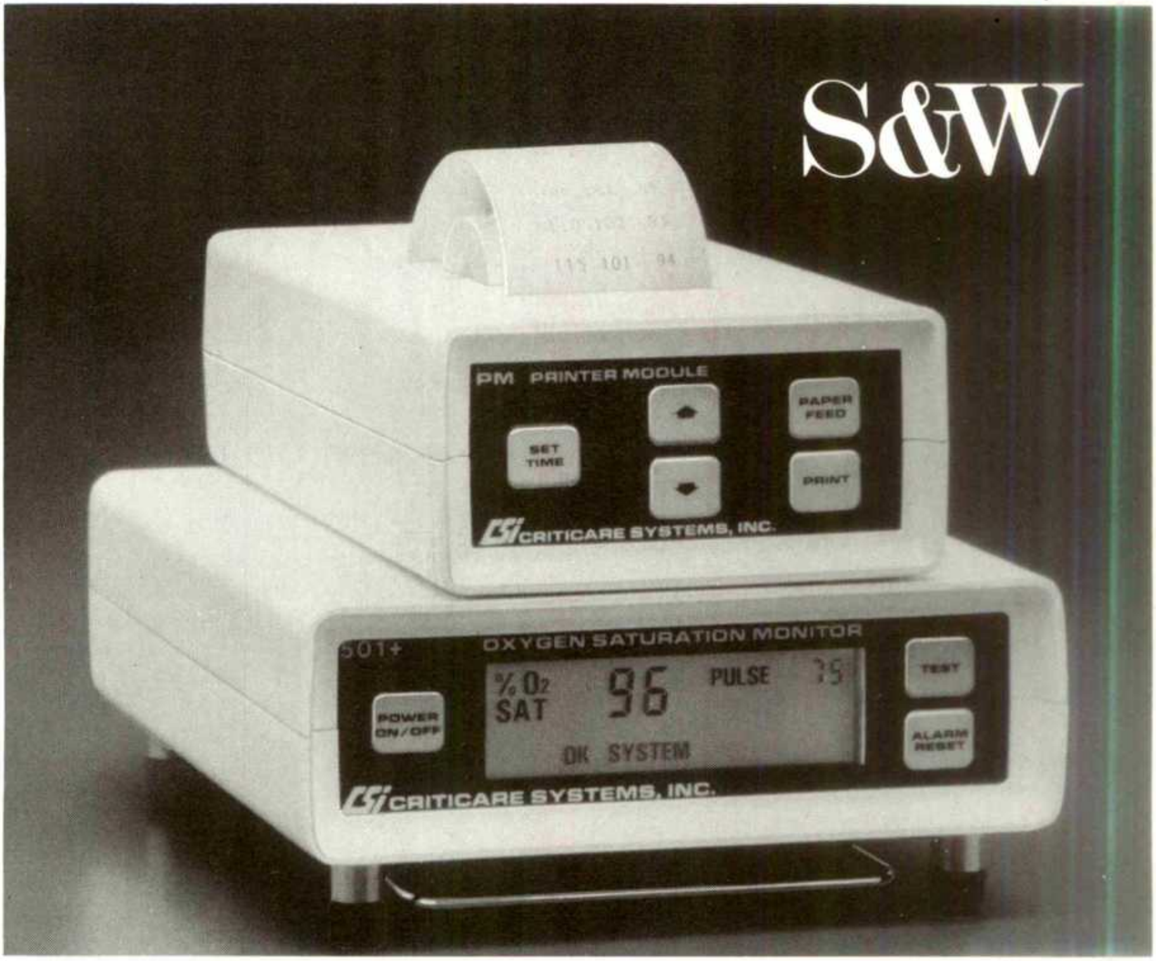

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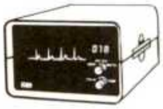

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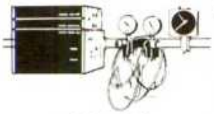

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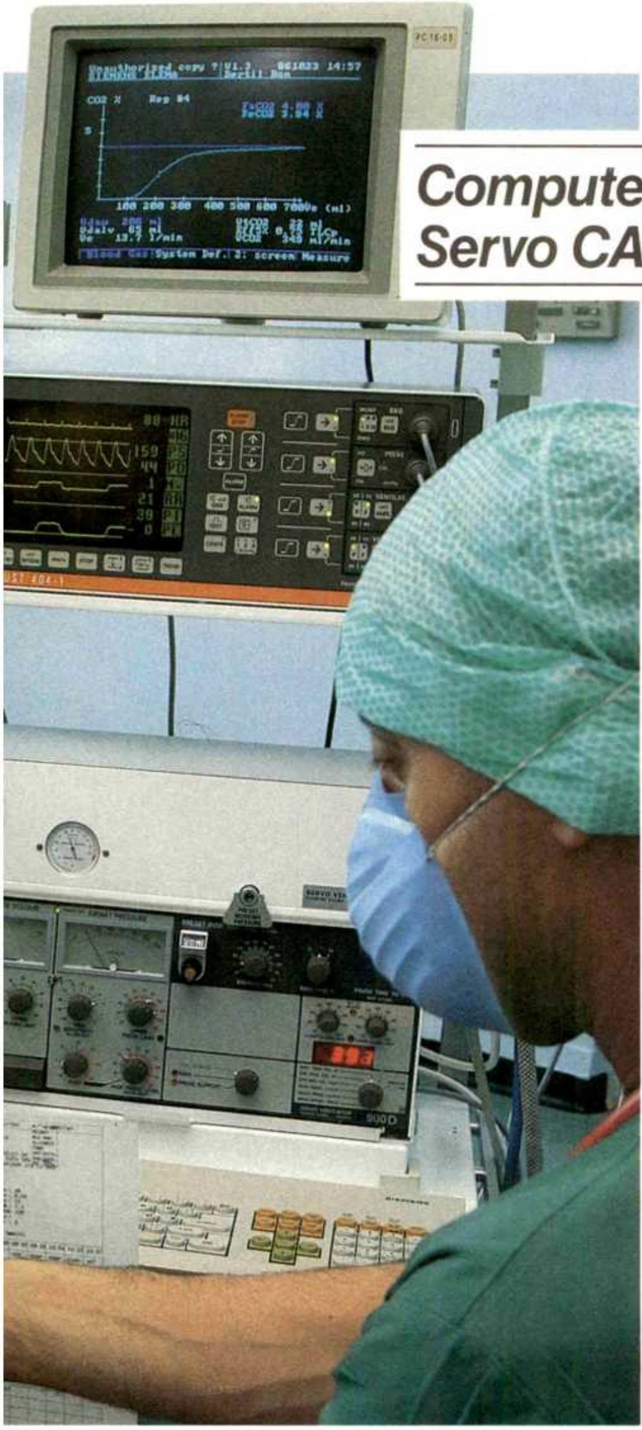

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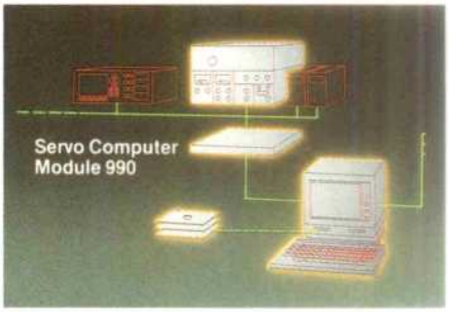

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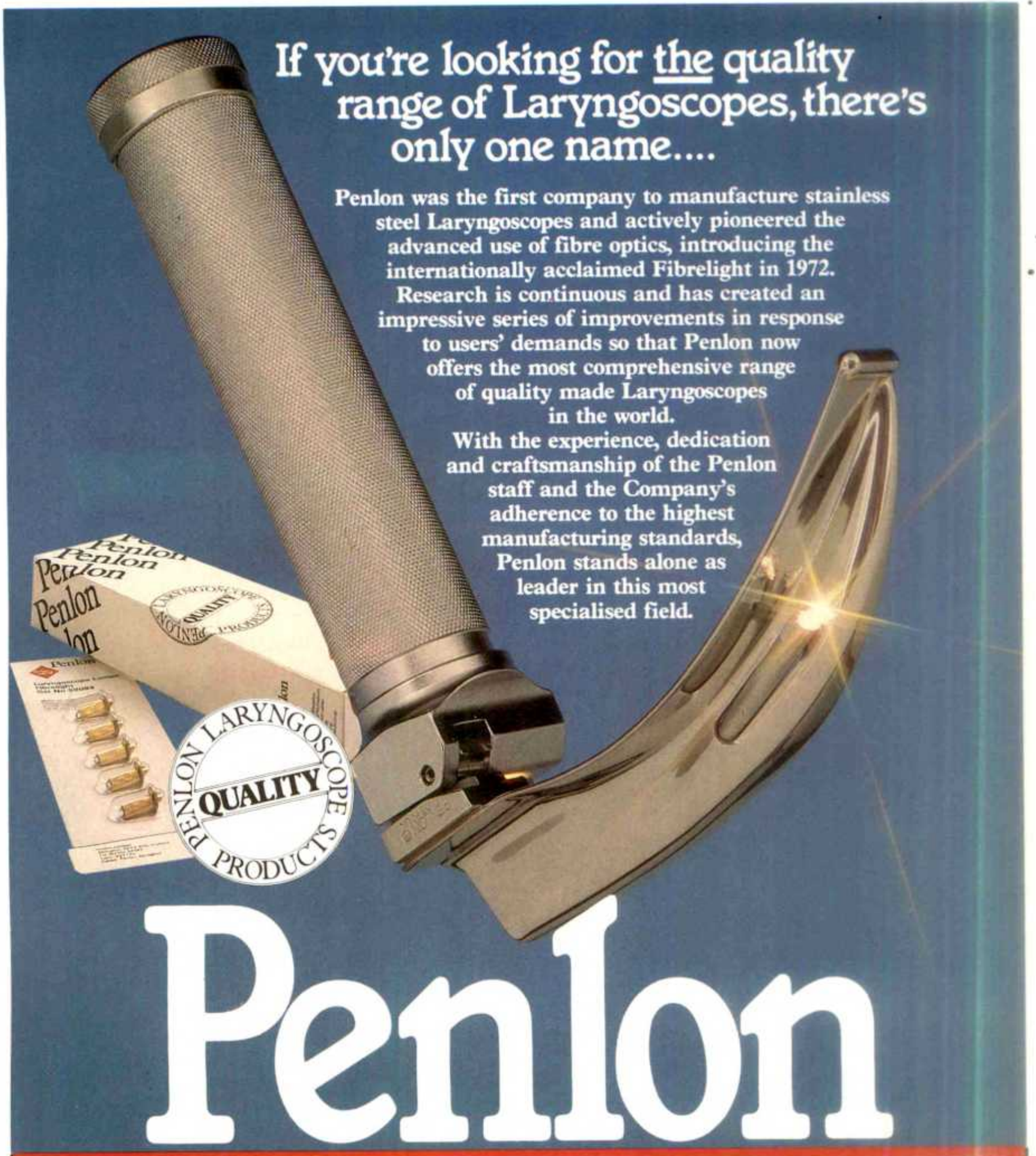

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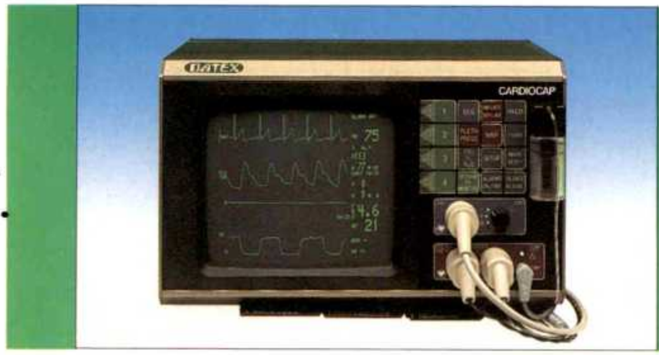

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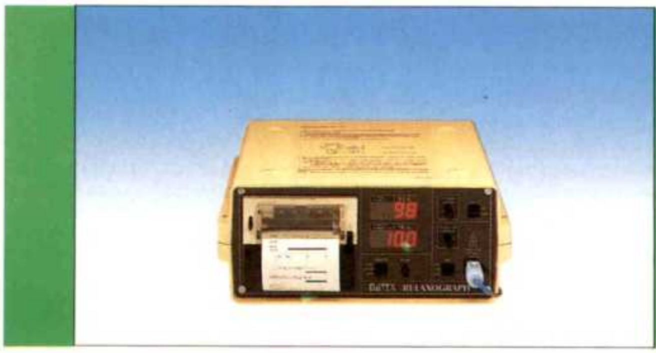

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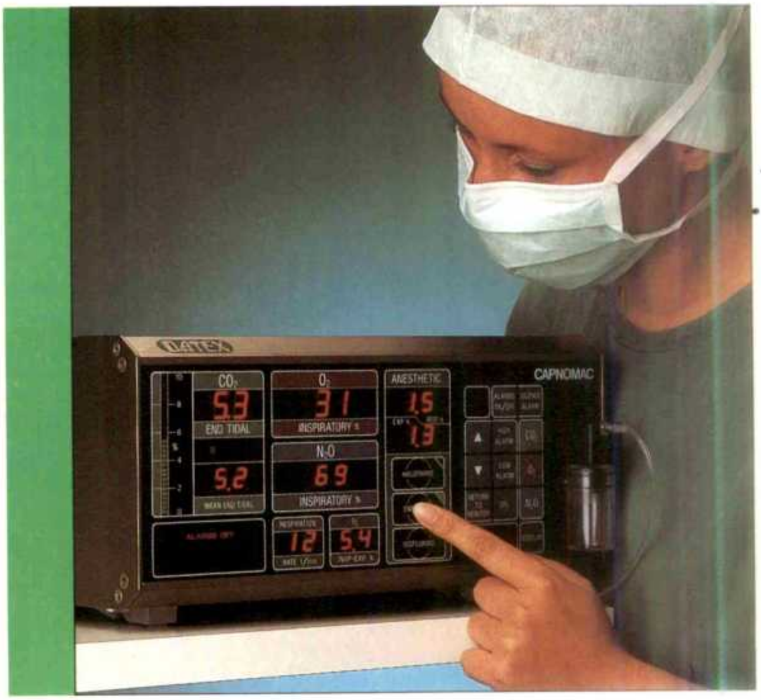

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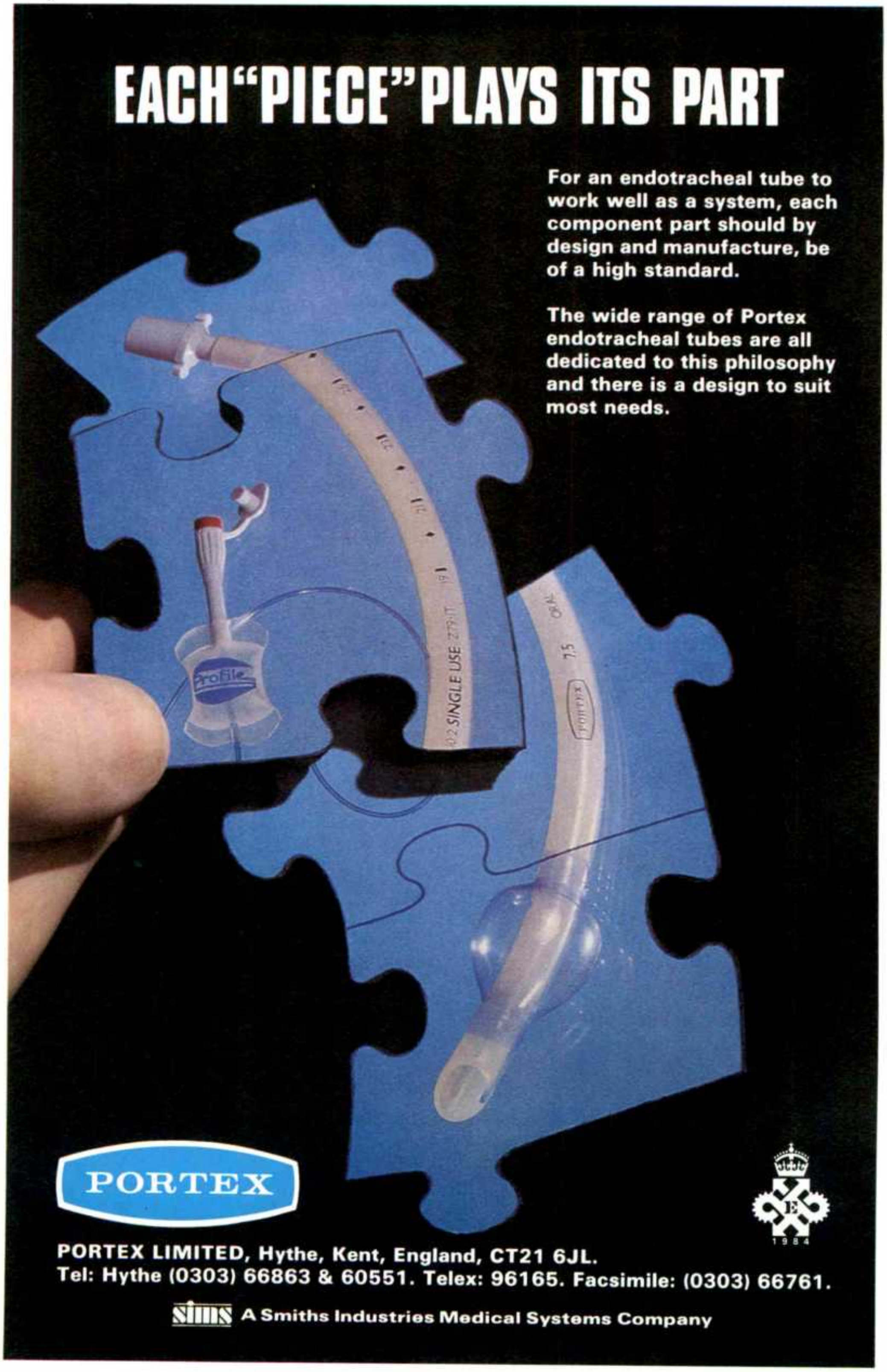

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 59, No. 3 MARCH 1987

EDITORIAL

TOWARDS SAFER ANAESTHESIA IN OBSTETRICS

Just over 30 years ago the Department of Health and Social Security in England and Wales set up a mechanism whereby the details of every death in relation to pregnancy and delivery (and, indeed, to the early puerperal period) was reported anonymously to two assessors—one of whom was concerned with the obstetric details and the other with the anaesthetic.

Every 3 years since 1956 an analysis of the deaths in each triennium has been conducted. The *Report on the Confidential Enquiries into Maternal Deaths in England and Wales 1979–81* (1986) is the most recent of these. (It is a pity that such a long interval has elapsed between the occurrences upon which it comments and the present date.) As its title implies ("Confidential Enquiry"), the reporters have concerned themselves mainly with matters relating to the practice of obstetrics but, as in the preceding years, a discussion of deaths associated with anaesthesia has been included. In the years to which the report refers anaesthesia was the second most common cause of maternal mortality, and pulmonary embolism, which was the commonest cause of all, had fallen from first to third place; hypertensive states (including toxaemia) were the principal cause. There were 29 patients in whom death was either directly attributable to anaesthesia, or in whom the administration of an anaesthetic made some contribution to the fatality. This compares with 40 deaths in 1976–78, and 37 in 1973–75. For the first time, too, there was a substantial reduction in the overall death rate per million pregnancies, which decreased from 13.5 in 1970–72 to 9.0 in 1979–81. This would seem to imply that real progress has been made in improving the provision of anaesthesia for obstetric patients—the more so as the number of Caesarean sections has increased.

As far as the individual causes of death are concerned, however, the report gives less ground for optimism: eight patients died from the effects of the inhalation of stomach contents. In six of these, cricoid pressure had been applied before intubation of the trachea. Even so, five of these patients developed aspiration pneumonitis. All of these were stated to have had magnesium trisilicate mixture during labour and before operation. This observation emphasizes the fact that magnesium trisilicate or other similar alkali may perhaps be irritant if it is inhaled (Bond, Stoelting and Gupta, 1979). There is an additional problem that the free administration of this mixture to increase the pH of the gastric juice may add to the volume of fluid in the stomach in patients with gastric stasis, especially if inadequate mixing of gastric contents occurs, so much so that the report now suggests that H_2-receptor antagonists should be used to reduce acidity, and that no food or fluids should be given by mouth during labour. Consideration should also be given to emptying the stomach with an oesophageal tube before anaesthesia, particularly where large doses of narcotics have been given during labour. This represented a very considerable shift of view. Although it is now customary to administer "clear" antacids to neutralize the acid already in the stomach, this is not mentioned in the report since the report relates, naturally, to the practice of obstetric anaesthesia in the years to which it applies.

Difficulty with intubation emerges in this report as a major potential cause of aspiration, and of fatalities for other reasons. In two patients the inhalation of gastric content occurred during a difficult intubation. In four patients difficulty in intubation resulted in the passage of the tube into the oesophagus and this misplacement was not recognized until irreversible damage had been done to the patient. Indeed, in four of these eight patients death was the result of persistence with attempts at tracheal intubation, to the point of hypoxia in a patient who was technically difficult to intubate.

Two points emerge in relation to inadvertent oesophageal intubation. Preoxygenation properly performed produces a reserve of oxygen in the lung alveoli which may not be exhausted for some considerable time, and during this time the fact that the tube is in the oesophagus will not give rise to cyanosis and may pass unnoticed (Howells, 1985). Although the report does not comment on it, others have suggested that the use of a carbon dioxide analyser may provide early diagnosis of inadvertent oesophageal intubation, with consequent benefit to the patient (Linko, Palhesimo and Tammisto, 1983).

As in previous reports, the danger of unrecognized blood loss is mentioned and attention drawn to the necessity of having a drill for the management of severe haemorrhage, including the provision of extra staff in an emergency, the ready supply of blood and, above all, staff properly experienced in the management and monitoring of blood loss.

As in so many previous reports, the need for effective communication between junior members of staff and their consultants is mentioned. Attention is also drawn to the fact that a tracheal tube is by no means a necessity for anaesthesia for Caesarean section. Better a live patient with minimal soiling of the lungs with regurgitated gastric content than a patient dead from asphyxia arising from prolonged and misguided attempts to pass a tracheal tube at all costs.

This report emphasizes the need for a high standard of postoperative care in obstetrics as in other fields, especially as patients are frequently given long-acting neuromuscular blocking drugs or powerful respiratory depressants, or both. Such patients are liable to develop respiratory insufficiency. If fatalities are to be avoided, a high standard of post-anaesthetic monitoring is required.

A. R. Hunter

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Br. J. Anaesth. (1987), 59, 277–282

EFFECT OF ISOFLURANE ON THE AUDITORY EVOKED RESPONSE IN MAN

C. P. H. HENEGHAN, C. THORNTON, M. NAVARATNARAJAH AND J. G. JONES

SUMMARY

We have examined the effects of isoflurane (0.6–2.9% end-tidal) on the auditory evoked response (AER) in six patients before elective surgery. Isoflurane produced significant dose-related changes in the AER: reductions in amplitude and increases in latency of the cortical waves Pa and Nb, and increases in the latency of the brainstem waves III and V. When isoflurane was compared with halothane and enflurane using an MAC-based comparison, we found no differences in the effect of the three agents on the amplitude of the early cortical waves, although the latencies showed significant differences. The consistent dose-related effect on the amplitudes of the cortical waves implies that the AER could be a promising index of the depth of anaesthesia.

The use of sympathetic and haemodynamic signs to assess the depth of anaesthesia in paralysed patients is unsatisfactory, and results in an incidence of awareness of up to 7% (Breckenridge and Aitkenhead, 1983). The development of i.v. anaesthetic drugs with minimal side effects may compound the problem because weight-related infusion rates can produce widely different blood concentrations (Sear and Prys-Roberts, 1979; Thornton et al., 1985, 1986). In these circumstances awareness or overdose are equally likely, and are undetectable in the absence of side effects (Hug, 1985). There is, therefore, a need for an objective measure of the depth of anaesthesia and, in an attempt to find such a measure, we have been studying the effects of general anaesthetic drugs on the auditory evoked response (AER).

The characteristics of an ideal index of the depth of anaesthesia include the following: the index must be graded, so that the approach of awareness can be detected before its onset; it should be applicable to all anaesthetic agents, and to mixtures of agents; and it should be unaffected by non-anaesthetic drugs, such as β-adrenoceptor blocking agents and myoneural blocking drugs.

Initially, we attempted to establish whether the AER was affected similarly by the commonly used anaesthetic drugs—since there is evidence that different anaesthetic agents affect the somatosensory evoked response differently. For example, enflurane appears to increase the amplitude of some waves, which are decreased by most other agents (Clark and Rosner, 1973). So far, we have shown (Thornton et al., 1983, 1984, 1985, 1986) that halothane, enflurane, etomidate and Althesin had similar effects on the early cortical (middle latency) components of the AER, decreasing the amplitudes and increasing the latencies of waves Pa and Nb.

We then wanted to test whether the effects of the inhalation agents halothane, enflurane and isoflurane on the AER were related to their potencies as assessed by their MAC values. An earlier comparison of halothane and enflurane revealed that, although halothane had more of an effect on most waves than did enflurane at the same end-tidal concentration, there were some discrepancies when precise MAC-related comparisons were made. It was hoped that the present study would elucidate this problem.

C. P. H. HENEGHAN, B.A., B.M., B.CH., F.F.A.R.C.S.; C. THORNTON, B.SC., M.SC.; M. NAVARATNARAJAH, M.B., B.S., F.F.A.R.C.S.; J. G. JONES*, M.D., F.R.C.P., F.F.A.R.C.S.; Division of Anaesthesia, Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex AH1 3UJ. Accepted for Publication: August 4, 1986.

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A final reason for this project was to look at sites of action of anaesthetics. The AER is particularly useful for this, since the sites of generation of many of the waves have been located in the brain stem and cortex (Maurer, Leitner and Schafer, 1980). There is evidence that the important site of anaesthetic action of all these drugs is rostral to the brainstem, possibly cortical, and this concept is supported by studies of the effects of etomidate and Althesin on regional brain metabolism (Davis et al., 1984; R. A. Hawkins, personal communication).

We wished to determine whether the effects of isoflurane were similar to those of the other inhalation agents and, accordingly, have investigated its effect on the brainstem as well as the cortex.

PATIENTS AND METHODS

Six patients with normal hearing (aged 18–45 yr), scheduled for elective surgery expected to last 1–2 h, gave informed consent to participate in the study—the design of which had been approved by the Harrow District Ethical Committee. After premedication with morphine 10 mg and atropine 0.6 mg i.m., anaesthesia was induced with thiopentone 2–4 mg kg^{-1}. Pancuronium 0.1 mg kg^{-1} was given, the trachea intubated and the lungs ventilated with 70% nitrous oxide in oxygen, isoflurane being added to the gas mixture as described below. Fresh gas flow and, hence, ventilation was adjusted to keep end-tidal carbon dioxide constant in the range 5.0–5.6 kPa (38–42 mm Hg) as measured with a Hewlett-Packard 47201A in-line carbon dioxide analyser. Temperature, measured with an oesophageal thermistor probe, was also kept constant, and heart rate and arterial pressure were monitored. An arterial pressure of less than 90 mm Hg systolic was treated by the infusion i.v. of lactated Ringer's solution; a decrease in arterial pressure to less than 80 mm Hg systolic would have necessitated the cessation of the administration of isoflurane and, hence, the abandonment of the study.

At 7 min after the induction of anaesthesia, isoflurane was added to the fresh gas flow in concentrations which increased in five equal steps of 0.75% to a maximum of 3.75%, each inspired concentration being held for 10 min. The inspired and end-tidal concentrations were measured using an Engstrom EMMA, protected from the effect of water vapour by placing a condenser humidifier between the sensing probe and the patient.

The AER was recorded before and after the induction of anaesthesia, and in the second half of the 10 min at each inspired concentration of isoflurane. A 500-μs unidirectional rectangular wave pulse was generated by a Global Specialties Corporation 4001 pulse generator, and applied to accoustically shielded Telephonics TDH 39P headphones. This gave a binaural rarefraction click 75 dB above the normal hearing threshold, with a dominant frequency of 1 kHz. The EEG was recorded from silver–silver chloride disc electrodes, with the right and left mastoid and the inion placements being referred to the vertex. The EEG signal was amplified and filtered (25–3600 Hz) with a modified SLE 10/8 polygraph, and recorded on a Racal Store 4 FM tape recorder at 38 cm s^{-1} for subsequent analysis. The averaged AER for the 130-ms post-stimulus was derived from 2048 stimuli with a Datalab DL4000 averager. The AER variables examined were the latency and amplitude of waves I, III and V in the brainstem section of the response, and of waves Pa and Nb in the early cortical section. I–III, I–V and III–V intervals were also examined.

Regression analyses were carried out using the MINITAB programme (Ryan, Joiner and Ryan 1976), as previously described (Thornton et al., 1984). The MINITAB routines applied were: a test for a significant dose–response relationship with isoflurane for each variable for each patient, and then a derivation of a common dose–response slope representing all six patients, preceded by testing for parallelism. The comparison of dose–response slopes for the three different inhalation agents shown in table III was performed with a one-way analysis of variance on the individual patient's slopes.

All studies were completed before the start of surgery.

RESULTS

Table I shows the patients' demographic details. No study was discontinued on grounds of excessive hypotension (< 80 mm Hg systolic).

Increasing end-tidal concentrations of isoflurane increased the latency and reduced the amplitude of waves Pa and Nb in all patients. Figure 1 illustrates the early cortical waves in one patient, and in figure 2 Pa amplitude is plotted against end-tidal isoflurane concentration for all six patients. Increasing concentrations of isoflurane also increased the latency of brainstem waves III and V, as illustrated in figure 3.

TABLE I. *Demographic data. All surgery was elective, the female patients undergoing major gynaecological surgery, the male patient major orthopaedic surgery*

	Mean	SD
n	6	—
Age (yr)	36	4
Weight (kg)	63	9
Sex ratio (F/M)	5/1	—

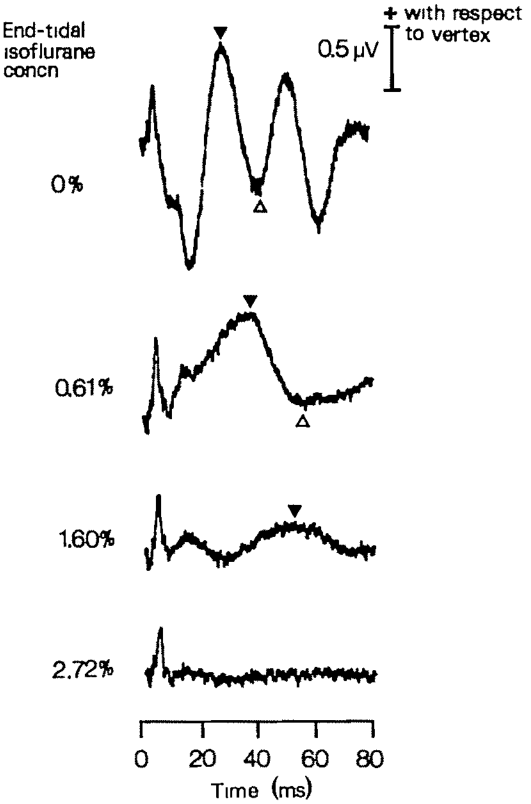

FIG. 1. Effect of increasing end-tidal isoflurane on the early cortical components of the AER. The latencies of Pa and Nb increase, and the amplitudes decrease, with increasing isoflurane concentration. ▼ = Pa; ▽ = Nb.

In one patient in whom surgery was delayed, isoflurane was discontinued to establish whether the observed effects were reversed when the end-tidal concentration of isoflurane was decreased; 15 min after discontinuing the isoflurane, the end-tidal concentration had decreased to the value obtained at the end of the first 10-min period, and the changes in the configuration of the waves had reversed almost completely.

Table II shows the mean slopes of the graphs of change of amplitude and latency of all the

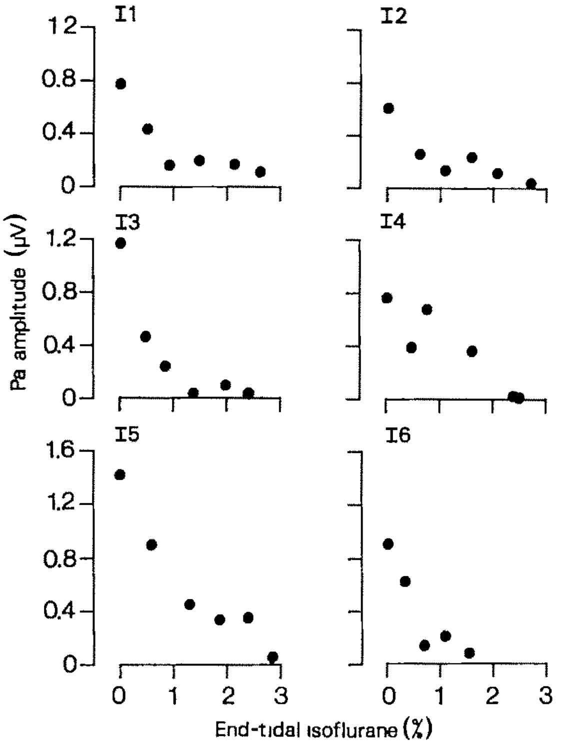

FIG. 2. Pa amplitude plotted against end-tidal isoflurane concentration, expressed both in % and MAC units. In all six patients Pa amplitude decreased as end-tidal isoflurane increased.

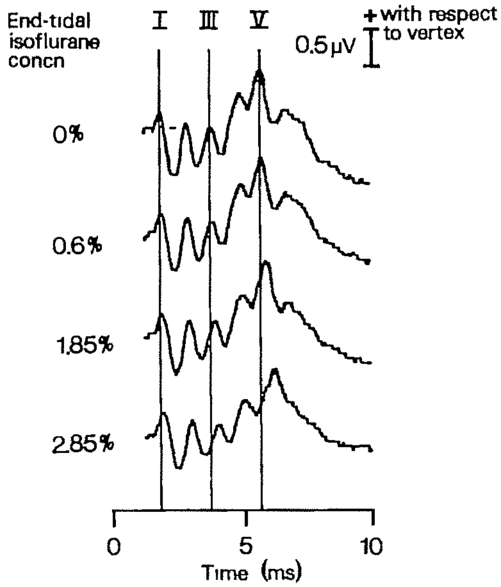

FIG. 3. Effect of increasing end-tidal isoflurane concentration on the brainstem components of the AER. Vertical lines are drawn through waves I, III and V at 0% isoflurane. In this patient III and V latency increased progressively with increasing end-tidal isoflurane.

TABLE II. *Relationship between end-tidal isoflurane concentration and latency and amplitude of waves indicated. Units of slopes of latencies and intervals are ms/% end-tidal isoflurane, and for amplitude μV/% end-tidal isoflurane. Significance:* **$P < 0.01$; *$0.1 > 0.1P > 0.05$; *ns = not significant*

Wave	Function	Slope	SEM	*P*
I	Latency	0.00	0.02	ns
III	Latency	0.22	0.05	*
V	Latency	0.32	0.04	**
Pa	Latency	18.7	2.4	**
Nb	Latency	29.6	3.4	**
I–III	Interval	0.22	0.06	ns
I–V	Interval	0.32	0.04	**
III–V	Interval	0.10	0.03	*
III	Amplitude	−0.02	0.01	ns
V	Amplitude	−0.04	0.01	ns
Pa	Amplitude	−0.21	0.03	**
Nb	Amplitude	−0.21	0.04	**

identified waves per unit change in end-tidal isoflurane concentration (%), together with *P* values for the difference of the slopes from zero. There were significant concentration-dependent changes in the latency of waves V, Pa and Nb, and the I–V interval. The changes in III latency, and III–V interval approached statistical significance. Table III shows the results from our previous study of the effects of halothane and enflurane on the AER compared with those of the present study. The results are MAC, rather than concentration, related. The effects of the three agents on III and V latency and Pa and Nb amplitude did not differ significantly between the three agents, although the latencies of Pa and Nb were affected significantly.

DISCUSSION

This study shows that isoflurane affects the auditory evoked response (AER) by increasing the latencies of waves III, V, Pa and Nb, and reducing the amplitudes of waves Pa and Nb. These effects were dose related, and similar in all patients.

We have shown that isoflurane has effects on the *early cortical* waves of the AER similar to those of all the anaesthetics we have previously studied (Thornton et al., 1983, 1984, 1985, 1986): halothane, enflurane, etomidate and Althesin all increased the latency and decreased the amplitude of the early cortical waves in the AER reversibly and in a dose- or concentration-related manner. This point is important in relation to the measurement of depth of anaesthesia, because a technqiue which can be utilized during routine general anaesthesia must be similarly affected by all anaesthetic drugs. Various other indices which have been considered as measures of depth of anaesthesia all share the disadvantage of being differently affected by different anaesthetics (Jones, Heneghan and Thornton, 1985). Specific examples of this are EEG–power spectral analysis, and its derivatives the compressed spectral array and the spectral edge. Enflurane also affects the somatosensory evoked response differently from other agents, increasing the size of the P_{100} cortical component which the other agents suppress (Clark and Rosner, 1973). This difference in effect is not a problem with the early cortical components of the AER, as all the agents that we have so far studied, and now isoflurane, consistently reduce the amplitude and increase the latency of early cortical (middle latency) waves (Thornton et al., 1983, 1984, 1985, 1986).

We have examined the potency relationship of the effects of the inhalation agents on the brain stem and early cortical waves in table III. (There is no measure of anaesthetic potency that applies to the i.v. agents.) The effects of isoflurane are compared with those of halothane and enflurane from our previous study (Thorton et al., 1984), using MAC-corrected effects. This was done by

TABLE III. *Comparison of the effects of isoflurane from the present study with those of halothane and enflurane (Thornton et al., 1984); results now expressed in MAC units rather than percentages (MAC values used: halothane 0.7%; enflurane 1.7%, isoflurane 1.2%)—thus units are ms/MAC unit, and μV/MAC unit, as appropriate. Values are means (SD). Different from halothane:* ***$P < 0.001$; *different from halothane and enflurane:* †††$P < 0.001$

Wave	Function	Halothane ($n = 6$)		Enflurane ($n = 6$)		Isoflurane ($n = 6$)	
III	Latency slope	0.23	(0.21)	0.27	(0.05)	0.26	(0.25)
V	Latency slope	0.23	(0.07)	0.40	(0.08)	0.37	(0.17)
Pa	Latency slope	6.8	(2.7)	20.1	(6.2)***	23.7	(4.9)***
Nb	Latency slope	8.9	(5.8)	18.3	(8.9)	37.1	(9.6)†††
Pa	Amplitude slope	−0.51	(0.15)	−0.43	(0.30)	−0.28	(0.14)
Nb	Amplitude slope	−0.23	(0.18)	−0.37	(0.23)	−0.27	(0.11)

comparing the slopes of III and V latency, and Pa and Nb latency and amplitude plotted against MAC multiples rather than vapour concentration. If the effects of these drugs exactly corresponded with their MAC values, then the mean slope for each individual variable for each drug would be identical. The slopes for III and V latency, and for Pa and Nb amplitude are not significantly different between the three agents, but there are differences for Pa and Nb latency. This indicates a quantitative difference in the effects of these drugs on the latencies of the early cortical waves, which in turn suggests that these variables will not be useful indices of the depth of anaesthesia. This is not the only interpretation; since these results are based upon small samples, these may be chance findings. The amplitude of waves Pa and Nb are the most promising candidates in the search for an index of depth of anaesthesia because they were not quantitatively differently affected by the three volatile agents and were qualitatively similarly affected by etomidate and Althesin.

Isoflurane has effects on the *brainstem* components of the AER similar to those of halothane and enflurane (Thornton et al., 1983, 1984), which also increase the latencies of the brainstem peaks III and V. This finding is in accord with a recent report which showed that isoflurane increased the latencies of the brainstem peaks (Manninen, Lam and Nicholas, 1985). However, these authors reported that isoflurane in oxygen had no further effect on the brainstem waves above a concentration of 1.5% end-tidal. On examination of these data, this was not the case for 1.5% enflurane in a 50% nitrous oxide mixture and, in our study, we found that with 70% nitrous oxide in oxygen there were increasing effects of isoflurane even up to 2.85% (fig. 3).

The similar effect of isoflurane, halothane and enflurane on the brainstem AER is in contrast to that of the i.v. agents etomidate (Thornton et al., 1985) and Althesin (Thornton et al., 1986), which exhibited no effect on the brainstem AER at a time when they had produced profound depression of the early cortical waves. This relative sparing of the brainstem AER occurs with two agents which are noted for their minimal effect on respiratory and cardiovascular homeostasis, and we have previously speculated (Thornton et al., 1985, 1986) that these effects may be related. The homeostatic stability observed during anaesthesia with these agents may result in part from an absence of effect on the brainstem.

These regional differences in the effects of different anaesthetics on the AER correspond to the regional differences in their effects on cerebral metabolism—despite the intense controversy that has surrounded the methods for measuring regional brain metabolism (Crosby and Sokoloff, 1983; Hawkins, Hass and Ransohoff, 1983). Hawkins and Biebuyck (1980) have shown that halothane reduces metabolism in both the medial geniculate and the inferior colliculus in the rat, and the effect on the inferior colliculus was also observed in primates (Shapiro et al., 1978). However, Althesin (Davis et al., 1984) and etomidate (R. A. Hawkins, personal communication) had a negligible effect on the inferior colliculus and more caudal parts of the auditory pathway compared with a striking effect on the cortex. This is not to say that all i.v. agents spare the brainstem. Barbiturates reduce uniformly the metabolism of the brain (Sokoloff, 1981), although the effect of thiopentone on the AER has not been studied in detail. Our own observations and those of others (M. F. M. James, personal communication) indicate substantial effects of thiopentone on both the brain stem and cortical components of the AER. Methohexitone produces a significant increase in wave V latency (Kriss, Prasher and Pratt, 1982).

We conclude that all the anaesthetics that we have studied so far have a dose-related effect on the cortical part of the AER, whereas some spare the brain stem. These observations, together with studies of regional brain metabolism, lend support to the concept that loss of consciousness in anaesthesia may be more closely related to depression of cortical rather than brain stem function, and that this may be measured using the cortical components of the AER.

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DOSE REQUIREMENTS OF PROPOFOL BY INFUSION DURING NITROUS OXIDE ANAESTHESIA IN MAN

II: Patients Premedicated with Lorazepam

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C. R. MONK AND M. H. FAROQUI

SUMMARY

The infusion rate of propofol required to supplement 67% nitrous oxide in oxygen to maintain surgical anaesthesia was determined in 72 patients premedicated with lorazepam. Following an induction dose of propofol 2 mg kg^{-1}, groups of eight patients received an infusion of propofol varying from 60 to 200 µg kg^{-1} min^{-1}. Probit analysis was used to determine the ED$_{50}$ (130 µg kg^{-1} min^{-1}; 95% confidence limits: 106–167 µg kg^{-1} min^{-1}) and ED$_{95}$ (348 µg kg^{-1} min^{-1}; 95% confidence limits: 233–1296 µg kg^{-1} min^{-1}) for propofol infusion. Whole blood propofol concentrations at the time of surgical incision correlated strongly with the infusion rate, giving an EC$_{50}$ value of 2.5 µg ml^{-1}, and an EC$_{95}$ value of 5.92 µg ml^{-1}. There was no significant correlation between the rate of infusion of propofol, or the total propofol dose, and the times to response to command, or to recall of birthdate.

Propofol (2,6 di-isopropyl phenol) has been reformulated in an aqueous emulsion in an attempt to reduce the venous sequelae, pain on injection and allergic reactions which were associated with the original Cremophor EL formulation. The dose required to induce anaesthesia with the new formulation is approximately 20% more than that for the previous formulation (Cummings et al., 1984). In patients premedicated with morphine, and breathing 67% nitrous oxide in oxygen, we found that the minimum infusion rate required to prevent a response to the initial surgical incision in 50% of patients (ED$_{50}$) was 53.8 µg kg^{-1} min^{-1} with the present formulation (Spelina et al., 1986) compared with 51 µg kg^{-1} min^{-1} with the previous formulation (Prys-Roberts, Sear and Adam, 1981).

In previous studies of infusion anaesthesia, the ED$_{50}$ values for methohexitone and Althesin in patients premedicated with a benzodiazepine were 30% higher than for similar patients premedicated with morphine (Sear et al., 1983). We predicted that the ED$_{50}$ for the aqueous emulsion formulation of propofol, in patients premedicated with a benzodiazepine, would be similar to that for methohexitone in benzodiazepine premedicated patients, based on the premise that the ED$_{50}$ values for both propofol and methohexitone following premedication with morphine have been shown to be of the same order (53.8 and 48.8 µg kg^{-1} min^{-1}, respectively).

The present study was designed to determine the dose requirement for propofol in patients premedicated with lorazepam, and breathing 67% nitrous oxide in oxygen.

PATIENTS AND METHODS

The patients studied (ASA groups I or II; age range 18–70 yr) were presenting for body surface surgery. Written informed consent was obtained following explanation of the study which was approved by the District Ethics Committee and the Committee on Safety of Medicines. Our original plan was to study five groups of eight patients randomly allocated to receive propofol by infusion at 60, 70, 80, 90 or 100 µg kg^{-1} min^{-1}. Early results indicated that the predicted infusion

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range was too low, and that we would have to limit the numbers of patients infused at these lower rates; further groups of eight patients each were infused at 110, 120, 140, 160, 180 and 200 $\mu g\ kg^{-1}\ min^{-1}$.

The patients were premedicated with lorazepam 2–3 mg by mouth (0.04 $mg\ kg^{-1}$ rounded to the nearest whole number) at least 1 h before the induction of anaesthesia. On arrival of the patient in the anaesthetic room, a cannula was inserted to a peripheral vein under local anaesthesia, this being used solely for induction (with propofol), and for the maintenance infusion of propofol. A baseline (preoperative) peripheral venous blood sample was taken to demonstrate absence of propofol. The electrocardiogram was monitored from a CM5 lead configuration, and arterial pressures were measured and recorded with a Dinamap 845 (Critikon). Anaesthesia was induced with propofol 2.0 $mg\ kg^{-1}$ given over 20 s followed immediately by an infusion of propofol 10 $mg\ ml^{-1}$ from a 60-ml syringe driven by a Vickers Treonic IP3 syringe pump. The rate was determined according to the dosage group to which the patient had been allocated.

The time taken for the induction of anaesthesia following the end of the initial injection was noted and during this time the patient was asked to report any pain or other unpleasant sensation. The presence and duration of apnoea was noted. Throughout the duration of the infusion, the patient breathed spontaneously, 67% nitrous oxide in oxygen being supplied through a Mapleson A breathing system. If required, an endotracheal tube was passed 1 min after giving suxamethonium 1 $mg\ kg^{-1}$. A period of at least 30 min was allowed to elapse before the initial surgical incision, and any movement in response to this noted and the patient was designated as a mover or non-mover. A further venous blood sample was taken for measurement of whole blood propofol concentration (by high pressure liquid chromatography with fluorescence detection, using a modification of the method described by Adam and colleagues (1981)). If the patient moved, a 10-mg incremental dose of propofol or fentanyl 0.10–0.20 mg, or both, was administered at the discretion of the anaesthetist. Fentanyl 25–200 μg was administered to 32 patients, and 15 patients received either halothane (0.5–1.0% inspired concentration) or fentanyl plus 0.5–1.0% halothane for periods between 5 and 45 min, after the move/no move response had been determined.

At the end of surgery, the infusion of propofol and the administration of nitrous oxide were discontinued simultaneously. For those patients who received propofol alone, or propofol and fentanyl, the times were noted between stopping the infusion and (a) the patient's first response to the command to open the eyes and (b) recall of the correct date of birth.

The numbers of patients moving or not moving at each infusion rate were subjected to Probit analysis (Litchfield and Wilcoxon, 1949), to yield values for ED_{50} and ED_{95} and their 95% confidence limits. Linear regressions were derived between the times to (a) response to command and (b) recall of birthdate, and the total dose of propofol, and the duration of the infusion.

RESULTS

Seventy-two patients (36 male) aged 18–70 yr and weighing 47–98 kg were studied. Sixteen patients (22.2%) complained of some pain on injection and 13 more (18%) of some other sensation such as tingling or change in temperature. Only two patients were inadequately anaesthetized by the induction dose and the median induction time for the others was 24.9 s (range 8–85 s). Apnoea occurred in 63 patients (87.5%) with a mean duration of 65.8 s and a maximum duration of 147 s. Of these who did not stop breathing, only seven were adequately anaesthetized by the induction dose. No patient recalled any events during anaesthesia and surgery, and none showed any venous sequelae in the postperative period. Only 37 patients (51.4%) received propofol alone, and the majority of these required one or more extra doses to supplement the infusion. For those who received propofol alone, the median times between turning off the infusion and opening of eyes to command, or recalling their correct date of birth were 14.9 min (range 2–61) and 19.1 min (range 4–91), respectively. There were no significant correlations between these recovery times and either the total dose received or the infusion rate (table I).

Eleven infusion rates were studied. The lower dose groups were not completed once it was realized that most of the patients were moving at infusion rates less than 100 $\mu g\ kg^{-1}\ min^{-1}$. Figure 1 shows the Probit diagram relating the number of movers/non-movers and the infusion rate of propofol. The ED_{50} derived from this relationship was 130 $\mu g\ kg^{-1}\ min^{-1}$ (95% confidence limits

TABLE I. *Duration of anaesthesia and surgery and the total dose of propofol given (mean ± SD); times from end of anaesthesia to eye opening and recall of birthdate (median and range) in 56 patients each receiving propofol (±fentanyl) by continuous infusion at one of 11 different rates to supplement anaesthesia maintained with 67% nitrous oxide. (Sixteen further patients received halothane and are not included.)* n = *Number of patients in group*

	Infusion rate (μg kg⁻¹ min⁻¹)										
	60 ($n=4$)	70 ($n=3$)	80 ($n=7$)	90 ($n=5$)	100 ($n=4$)	110 ($n=6$)	120 ($n=7$)	140 ($n=8$)	160 ($n=6$)	180 ($n=3$)	200 ($n=3$)
Anaesthesia	121.8	86.3	103.4	77.8	67.8	64.2	54.4	69.8	77.3	94.7	63.3
(min)	±39.1	±11.7	±42.7	±29.1	±8.1	±9.5	±19.0	±28.6	±81	±33.7	±16.2
Surgery	60.3	26.0	55.6	33.6	36.5	25.5	15.1	15.6	32.7	30.7	31.7
(min)	±32.9	±19.3	±31.8	±29.1	±10.1	±8.6	±6.6	±10.2	±13.1	±17.5	±17.0
Total dose	687.5	516.0	692.3	698.4	545.5	611.0	605.4	853.0	450.8	1316.0	893.0
(mg)	±159.6	±41.3	±41.3	±281.8	±53.5	±163.1	±191.6	±366.2	±152.4	±657.3	±432.1
Eyes open	5.5	10	11	15	11.5	23.5	17	19.5	22	38	18
(min)	(2–15)	(3–5)	(7–14)	(8–17)	(8–16)	(12–32)	(4–48)	(7–56)	(4–27)	(20–61)	(14–19)
Correct	8	13	11	16	13	25.5	23	23.5	27	45	22
birthdate (min)	(4–17)	(6–18)	(7–18)	(9–24)	(12–17)	(13–35)	(6–49)	(12–59)	(21–32)	(14–91)	(19–33)

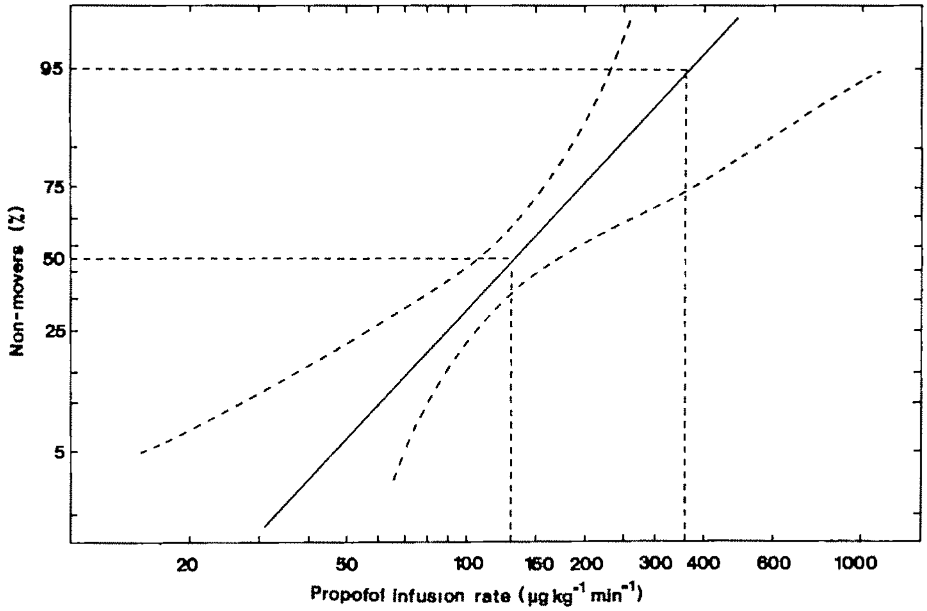

FIG. 1. Probit diagram relating percentage of patients moving or not moving as a function of the rate of infusion of propofol. Values in the text were derived for ED_{50} and ED_{95}.

106–167) and the ED_{95} was 348 μg kg⁻¹ min⁻¹ (95% confidence limits 233–1296).

Whole blood propofol concentrations were measured in 70 patients (fig. 2). There was a strong correlation ($r = 0.637$, $P < 0.001$) between whole blood propofol concentration (y) and the propofol infusion rate (x) at the time of the initial surgical incision, characterized by the equation:

$$y = 0.453 + 0.0157x.$$

From this regression, the whole blood concentration at the ED_{50} infusion rate was 2.50 μg ml⁻¹, and that at the ED_{95} infusion rate was 5.92 μg ml⁻¹.

DISCUSSION

Although the initial dose of 2 mg kg⁻¹ induced satisfactory anaesthesia in 97% of patients, there was a wider range of induction times and a higher

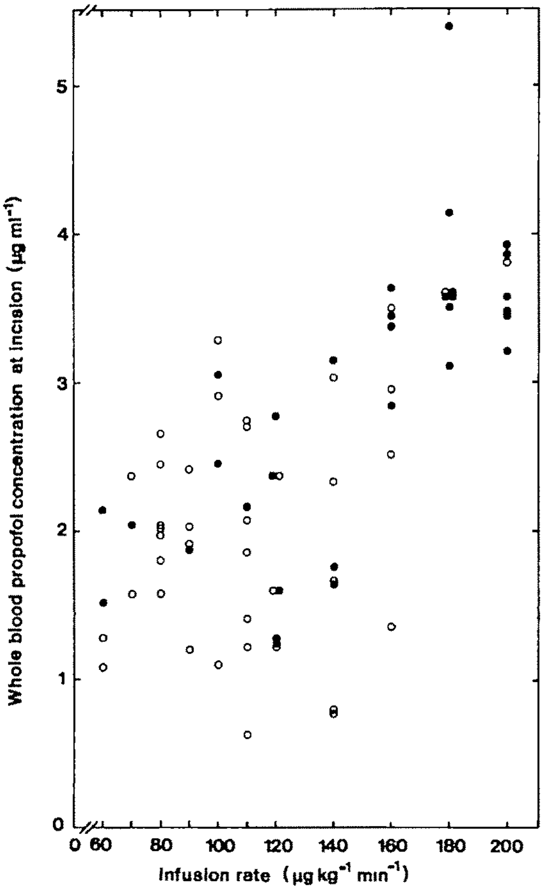

FIG. 2. Relationship between whole blood propofol concentrations at the time of the initial surgical incision (move/no move response) as a function of the propofol infusion rate. Open circles represent patients who moved, closed circles represent patients who did not move, in response to the initial surgical incision.

incidence of apnoea compared with our previous study of patients premedicated with morphine (Spelina et al., 1986). The incidence of pain on injection (22%) was slightly lower than that in the morphine-premedicated patients.

The ED_{50} and ED_{95} values for propofol (by infusion) in the present study were considerably higher than the values predicted on the basis of our previous studies (Sear et al., 1983) of Althesin and methohexitone. In those studies the ratios of the ED_{50} values for diazepam- or morphine-premedicated patients were 1.32 for patients anaesthetized with Althesin, and 1.35 for patients anaesthetized with methohexitone. If we compare the findings of the present study with those of Spelina and colleagues (1986) we find an ED_{50} ratio of 2.48, and an ED_{95} ratio of 2.38. The ratio of ED_{95}/ED_{50} in the present study was 1.99 compared with a ratio of 2.08 in the study by Spelina and coworkers (1986). Both these ratios for propofol are much higher than those found by Sear and co-workers (1983) for Althesin (1.34 in morphine-premedicated patients, 1.31 for diazepam-premedicated patients) and for methohexitone (1.55 for morphine-premedicated patients, 1.22 for diazepam-premedicated patients). Thus the dose–response curves for maintenance infusion rates are much flatter for propofol than for either Althesin or methohexitone, regardless of the premedication used.

In clinical practice, the ED_{95} is more useful, as it represents the infusion rate most likely to suppress movement of the patient in response to surgery. The main disadvantage of using propofol alone, to supplement nitrous oxide anaesthesia following lorazepam premedication, was that the median times to response to command (14.9 min), and recall of date of birth (19.1 min) were significantly longer than the equivalent times in patients premedicated with morphine (5.13 min and 7.00 min, respectively), even though the duration of anaesthesia was not significantly longer. We would recommend, therefore, that if an infusion of propofol is used to provide anaesthesia in patients premedicated with benzodiazepines, an opioid should be given before or during the infusion, or both, to minimize the required rate of infusion.

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STEREOPHOTOGRAMMETRIC ANALYSIS OF CHANGES IN BODY VOLUME ASSOCIATED WITH THE INDUCTION OF ANAESTHESIA

M. R. LOGAN, D. T. BROWN, I. NEWTON AND G. B. DRUMMOND

SUMMARY

Changes in the volume of the trunk were measured in seven supine patients, when anaesthesia was induced with thiopentone i.v. Stereophotograms were taken before and after induction and measurements of volume calculated from contour plots of a reconstructed stereo image. The changes in volume of the visible part of the trunk were between −846 and +505 ml. No systematic change in total or lower trunk ("abdominal") volume was evident, but there was a significant negative linear relationship ($r = -0.87$) *between upper trunk ("ribcage") volume change and obesity (expressed as actual weight/expected weight). Changes in volume were more evident in the upper parts of the supine subject, in both ribcage and abdomen* ($P < 0.05$).

The functional residual capacity (FRC) of the lungs has been shown to decrease by 200–700 ml (15–30%) on the induction of anaesthesia (Laws, 1968; Don, 1977). This change occurs rapidly and can be detected in the first few breaths taken after induction (Bergman, 1982). Attempts to measure the changes in external body dimensions that might be expected to reflect this sudden decrease in FRC have failed to detect consistent changes in the volumes of the thorax or abdomen (Vellody et al., 1978; Jones et al., 1979; Hedenstierna, Lofstrom and Lundh, 1981). For example, Hedenstierna and colleagues (1981), using the technique of body plethysmography, showed a 28% decrease in thoracic gas volume associated with the induction of anaesthesia, but were unable to find any significant change in the antero-posterior dimensions of the ribcage or abdomen as measured by magnetometer, strain gauge or inductive plethysmograph.

In those studies, measurements were made in one or two dimensions only, and any changes noted in limited parts of the body surface. The present study used the surveying technique of stereophotogrammetry to examine the three-dimensional changes of the surface of the body rather than specific points or linear dimensions of diameter or circumference.

PATIENTS AND METHODS

Ethical committee approval was obtained and consent was obtained from seven patients (ASA I and II). The patients' characteristics are shown in table I.

One hour before the start of the definitive study, each patient received temazepam 20 mg (by mouth) and a nasogastric tube was inserted. The patient was allowed to relax in the supine position on a mattress filled with polystyrene beads (Howmedica Vac-Pac). The air was then evacuated from the mattress to make a solid conforming mould underneath, and on the lower sides of, the patient's body. Two cameras mounted with parallel axes (Stereometric Officine—Gallileo A-Special) with an interaxial distance of 560 mm were mounted on a rigid gantry 1.6 m above the supine patient (fig. 1). Aviplot Pan 600 (13 × 8 cm) camera plates (Agfa-Gevaert) were used. These plates are intended for accurate photographic measurement techniques. They conformed to USA standard PH 1–23–1968 and the maximum vertical separation of the highest and lowest points of the emulsion side of the plate was 105 μm.

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TABLE I. *Characteristics of patients*

Patient No.	Sex	Age (yr)	Ht (cm)	Wt (kg)	% Expected weight
1	F	22	165	67.5	115
2	M	63	175	70	101
3	M	53	170	57	86
4	F	54	173	56	84
5	M	78	171	81	122
6	M	52	179	56	75
7	F	65	158	39	69

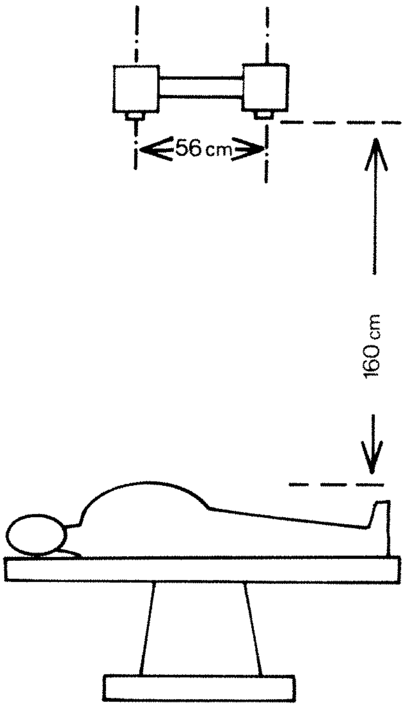

FIG. 1. Schematic view of the stereocamera positions.

To be certain that no skeletal movement occurred during the period of photography, the skin overlying the anterior superior iliac spines and the humeral heads was marked with ink. Four target plates were fixed firmly to the operating table at each corner of the photographic field to facilitate the later alignment of the photographic projections in the stereoplotter so that an accurate three-dimensional image could be produced. A 900-mm scale was placed beside the patient for calibration of the image. The patient's skin over the chest and abdomen was speckled with a brown surgical skin antiseptic, povidone iodine (Betadine), to increase the texture. This improved the visual detection of the surface of the projected three-dimensional image.

The nasogastric tube was attached to a fluid-filled pressure transducer system (Hewlett-Packard 267a) so that the phases of respiration could be gauged from the changes in gastric pressure displayed on an oscilloscope screen (Telequipment 51B). The patient was allowed some time to become comfortable and relaxed, and to achieve a stable state of quiet breathing. The first pair of stereophotographs was taken at end-expiration. Just before end-expiration, both camera shutters were opened electrically by solenoid triggers and, exactly at end-expiration, an electronic flash (Sunpac 33) was fired (manually) to provide illumination for synchronous exposure of the photographic plates, and the shutters were closed. New plates were loaded into the twin cameras. Anaesthesia was induced using a slow injection of thiopentone 2–4 mg kg^{-1} until loss of the eyelash reflex occurred. Oxygen 100% was administered from a Magill breathing system and a facemask while ensuring that airway obstruction was not present. A second set of stereophotographs was then taken in an identical manner, again at end-expiration when regular quiet respiration was present.

Each pair of developed negatives (fig. 2) was inserted to a stereoplotter (Wild A8) which recreated the relative orientation of the stereocamera axes at the time of photography using the metal targets placed around the patient for precise alignment. The plotter operator saw a three-dimensional stereoimage of the patient's chest and abdomen projected through a binocular optical system and could adjust the position of the image relative to the co-ordinate system of the plotter. He was able to manoeuvre the image so that the image of the fixed metal targets lay in defined points within the plotter co-ordinate system so that the same base plane was used for construction of a contour plot. The plot was made by use of a moveable marker that could be seen in relation to the stereoimage and moved by means of x, y and z co-ordinate controls. The marker was placed on the surface of the supine stereoimage and manoeuvred round it in a single horizontal z plane by moving the x and y controls only. These controls were geared to an x–y plotter so that a line representing the intersection of the set z plane and the surface of the stereoimage could be drawn. The z co-ordinate was then moved by 10 mm and another plot made. In this way, successive 10-mm

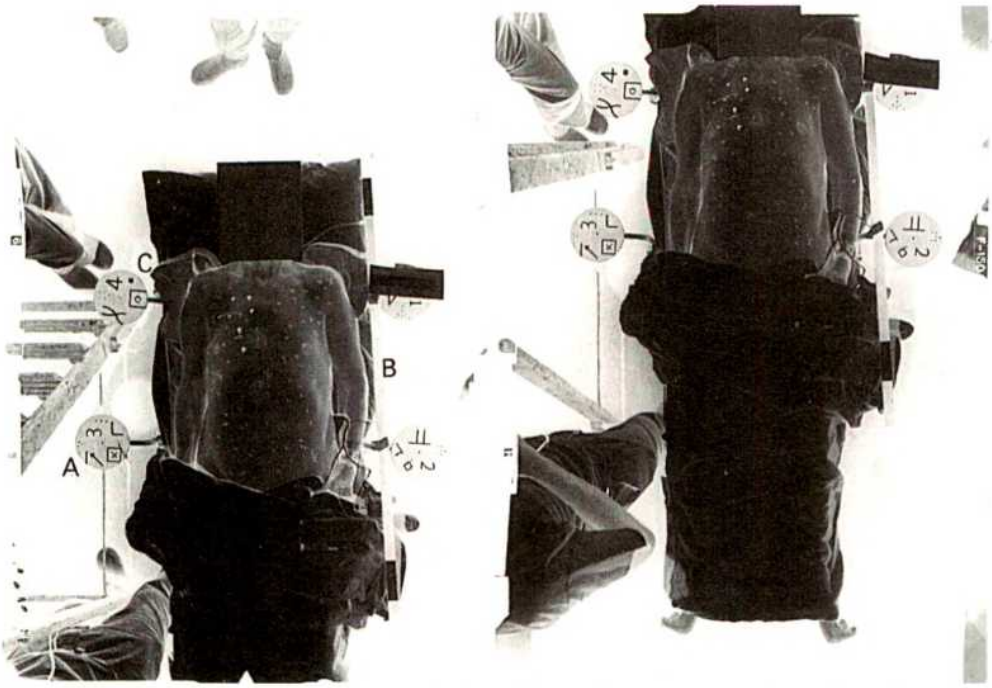

FIG. 2. A pair of stereophotographic negatives taken before induction, showing the different fields of view of the twin cameras. The skin is speckled with antiseptic. A = One of the four alignment targets. B = The linear scale. C = The rigid mattress.

contour lines were drawn to describe the shape of the stereoimage as a contour map (fig. 3). Each image was plotted from above the sternal notch to below the symphysis pubis. Each contour encompassed an area which was measured using a digitizing pad (Bit Pad One) connected to a BBC microcomputer. The area enclosed by each contour was calculated. In this way, a series of contour areas spaced 10 mm apart was generated and the enclosed volume was derived using the Trapezoidal Rule:

$$V = D/2[A_1+2(A_2+A_3\ldots+A_{n-1})+A_n]$$

where V = volume

D = distance between contours

A = area of contours 1, 2, … n

In this way, the volume of the patient's body that was visible to the camera before and after the induction of anaesthesia was determined by measuring from the points nearest the camera down to the last completely visible contour that was common to each pair of images. Between seven and 10 contours were available for measurement from each pair of images, the lowest contour being determined by the size and shape of the patient. Calculations of volume were made from sternal notch to symphysis pubis.

The contour measurements were made between the sternal notch and the pubic arch. This cranio–caudal dimension was divided into three equal segments and transverse lines drawn across to divide the contour plot into cephalad, middle and caudad parts.

The cephalad part consisted almost entirely of ribcage enclosing thoracic contents. The middle part comprised the epigastric abdominal wall, and the lower ribcage which overlies both thoracic and abdominal contents. The caudad part surrounded the abdominal contents only. Thus changes in volume in these three parts can be regarded, for comparative purposes only, as approximating to (a) pure ribcage, (b) a combination of ribcage and abdomen and (c) pure abdomen, respectively.

To allow assessment of the changes in volume of the upper and lower parts of the visible supine body shape, the measured volume was divided into two by choosing a contour which separated approximately equal volumes above and below

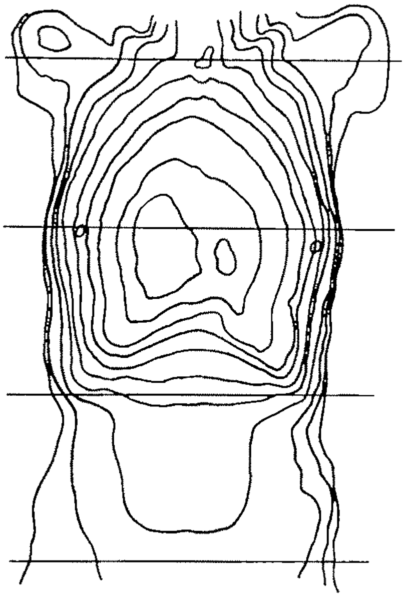

FIG. 3. A contour map showing the "ribcage", middle part and "abdomen" divisions.

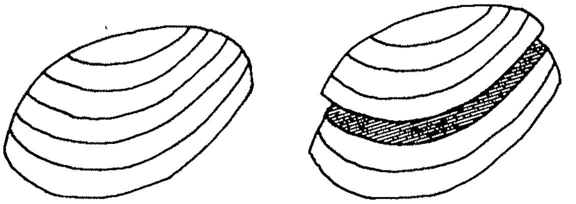

FIG. 4. Diagrammatic representation of upper and lower isoslices.

this plane (fig. 4). The volumes above and below this plane were calculated and termed "isoslices". These "isoslices" were then compared before and after the induction of anaesthesia.

For the purpose of analysis, obesity was expressed as the ratio of the actual weight of the patient to the average weight for subjects of the same age, height and sex (wt % expected) (Documenta Geigy, 1956).

Statistical analysis was by means of least square linear regression analysis and by paired *t* test as appropriate.

RESULTS

Table II shows the volumes measured and the changes that occurred on the induction of anaesthesia. The range of change in volume was from −846 ml to +505 ml. There was no systematic change in the volume of the body on the induction of anaesthesia. There was no relationship between total change in volume and body weight, height, sex or age.

There was no statistical difference between the volumes of the upper and lower isoslices. The mean change in the upper slice volume was 279 ± 189 ml and in the lower slice volume 114 ± 77 ml ($P < 0.05$). This suggests that most of the movement of body surface occurred overlying the upper slice and that lateral body wall movement contributed less to the volume change (fig. 5).

In four of the seven patients, the volumes of the cephalad, middle and caudad parts either increased or decreased together (table II). The maximum change in volume did not occur in any particular part, except that the middle part never contained the largest change in volume. The change in volume in each part was considered as a percentage of the volume of each part before anaesthesia. The percent changes in "abdominal" and middle segment volumes on induction of anaesthesia were not related to obesity (weight/average weight %). On the other hand, the percent

TABLE II. *Measurable volume (ml) of "Total body", "Ribcage", Middle segment and "Abdomen" before induction, and the changes in these volumes after the induction of anaesthesia*

Patient No.	"Total" (ml)		"Ribcage" (ml)		Mid segment (ml)		"Abdomen" (ml)	
	Awake	Change	Awake	Change	Awake	Change	Awake	Change
1	9088	−352	3373	−186	3467	−59	2248	−107
2	10983	+246	3711	−40	4816	+50	2454	+239
3	10202	+255	3323	+104	4547	−41	2332	+192
4	12788	+77	4297	+342	5366	−160	3125	−105
5	21290	−846	5450	−491	7931	−186	7909	−170
6	12397	−274	4781	−49	5620	−59	1996	−166
7	6456	+505	2386	+252	3431	+92	639	+161

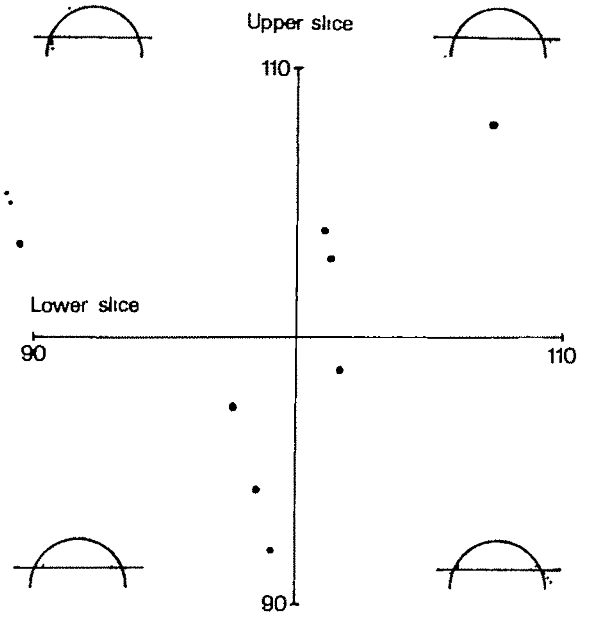

FIG. 5. The percent volume change of the upper slice plotted against the percent volume change of the lower slice. The diagrams in each quadrant represent the change in transverse sectional dimensions before and after anaesthesia (solid line: pre-induction; stippled line: post-induction).

change in volume of the "ribcage" correlated significantly with obesity (fig. 6) ($r = -0.87$).

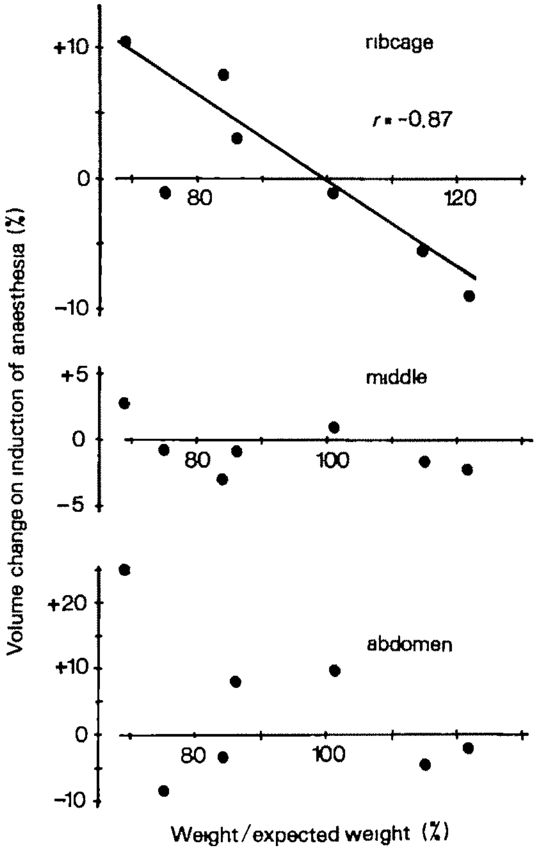

FIG. 6. The percent volume change in "ribcage", middle part and "abdomen" plotted against the patient's percent expected weight.

DISCUSSION

Stereophotogrammetry is the science of stereoscopic dimensional analysis from photographs. This surveying technique for appraising the surface structure of irregularly shaped objects gives a method of determining morphological and volumetric changes in the external surface of the body (Misken, 1956).

MacGregor, Newton and Gilder, (1971) tested the accuracy of the camera and stereoplotter used in this study at precisely the same focal distance of 1.6 m. Measurements were made of a plaster cast before and after removal of a portion of its visible volume. Stereogrammetric analysis of this volume change showed an overestimation of 6.75% compared with Archimedian and weighing estimates of the same removed volume. The degree of linear accuracy varied from a mean square error of ±0.07 mm, in the central areas where the curvatures were shallow, to ±0.74 mm at the subject's periphery where the surface curves steeply away from the camera. Peacock and colleagues (1984) found a linear accuracy similar to this with a related technique which used a projected optical contour mapping system of the thoraco-abdominal wall. We tested the reproducibility of the digitization by repeating each analysis. The mean difference in the digitized volumes was 15.5±9.5 ml.

By using the optical image of the patient, stereophotogrammetry holds several advantages over methods using magnetometers, inductive plethysmography or strain gauges. Because there is no physical attachment of the patient to the recording devices, coupling and interference with body surface shape or movement are eliminated. We were able to take measurements over the whole of the body surface that was visible to the camera, rather than from specific points on the body surface. Because the patient lay on a rigid mattress, movement of the axial skeleton was minimized. This was confirmed by the constant position of the marked bony prominences in reference to each other and to the target plates. This also suggests that the patients did not have a significant degree of skeletal muscle tone because of anxiety before induction.

Breathing movements were assessed by the nasogastric transducer system so that airway obstruction could be detected and corrected. This system was also used to time the manual firing of the electronic flash at end-expiration. The use of a single flash ensured that the exposure of the two photographic plates occurred at precisely the same time. Because of the shape of the body and the angle of view of its surface, a little less than half of the body surface was visible to the camera. The hidden dependent volumes of the body were supported by the rigid mattress, and only a small fraction of the body that was not seen by the camera was free to move. In this study, the change in volume of the upper slice of the visible body was markedly greater than that of the slice beneath. This would suggest that movement of the unsupported part of the portion not visible to the camera would be similarly small. This consideration is supported by the findings of Morgan, Gourlay and Denison, (1984) who found that 97 % of volume change in unrestrained supine subjects was in the upper surface.

In addition, volume analysis optical projection mapping systems are inherently less accurate at the periphery of the field as a result of the tangential incidence of light onto the curvature of the body. Morgan, Gourlay and Denison (1984) found differences between spirometric and optical analytical assessments of volume of up to 600 ml using a lateral projection technique. This apparent discrepancy may be explicable, since the upper slice contains the major part of the volume change and lies towards and beyond the periphery of their optical field and must include the eclipsed uppermost part of the body.

In a study of two volunteers before and after induction of anaesthesia using lateral cineradiographs, Froese and Bryan (1974) showed that the diaphragm moved cranially and suggested that this could account for the reduction in FRC that occurs on induction of anaesthesia. A widely held concept is that, because the abdominal contents can be considered incompressible, diaphragmatic movement results in an equal movement of the anterior abdominal wall (Konno and Mead, 1967). If this were so, a cranial movement of the diaphragm should have been associated with a reduction in the volume that we measured in the abdominal segment of the stereophotograph. This was not detected. However, in a more recent and more complex analysis, Mead and Loring (1982) have revised the concept that the abdominal contents are bounded by two moveable segments (the diaphragm and the abdominal wall). They suggest that there are three moveable segments of the container: the abdominal wall below the rib margins, and two distinct parts of the diaphragm. The upper part of the diaphragm lies below the lung and the lower, peripheral part of the diaphragm is apposed to the inner aspect of the lower ribcage and encloses abdominal contents. The relative proportions of these parts of the diaphragm depend on lung volume, but near FRC the proportion that is apposed to the ribcage is considerable. Consequently, an upward movement of the upper domed part of the diaphragm could occur as a result of a transfer of abdominal contents from the part encased by the lower ribcage, rather than being reflected by movement of the anterior abdominal wall. Consequently, our observations that the surface of the abdominal wall did not move inwards do not contradict the findings of Froese and Bryan (1974). Our division of the body surface into "ribcage", middle segment and "abdomen" was arbitrary for descriptive purposes only and did not take into account the true anatomical margins of the containers because of the complexity of the volume relationships between ribcage, diaphragm and abdominal wall.

It is difficult to explain the increase in total body volume detected in four of our patients. Since the volume of gas in the lungs (FRC) was likely to have decreased by 200–700 ml, a large increase must have occurred in some other content of the trunk. Hedenstierna, Johansson and Linde (1982) demonstrated a 50-ml central shift of blood from the limbs to the body on induction with thiopentone. This would only account for 5–20 % of the volume change seen in our patients if a 15–20 % decrease in FRC had occurred. Jones and co-workers (1979) noted a similar increase in body volume under anaesthesia using mercury-in-rubber strain gauges to measure the circumference of the chest wall and abdomen. However, measurements by this method must be interpreted with caution because a change in circumference does not necessarily lead to a proportional change in the area enclosed. Using modern radiographic imaging techniques (Dynamic Spatial Reconstruction Scanner), Krayer and his colleagues (1985) showed that on induction of anaesthesia (plus muscle paralysis), the external diameters of the ribcage changed in a fashion different from changes in the internal (pleural) dimensions. These changes could result in a net increase in external thoracic volume in spite of a decrease in internal volume, although the mechanism for this is uncertain. These writers attributed most of the decrease in lung volume to an increase in intrathoracic blood and that of the remainder to a change in the volume contained by the ribcage and diaphragm.

We found that, in patients of greater than ideal weight, the volume of the "ribcage" decreased on the induction of anaesthesia. Such patients have a greater reduction of FRC when moving into the supine position. Perhaps obese subjects develop some tonic intercostal muscle activity when they become supine, to prevent too great a reduction in FRC. Anaesthesia may reduce or abolish this activity and this could contribute to the decrease in FRC. The increase in intra-abdominal pressure seen in overweight subjects when anaesthesia is induced would support this thesis (Drummond and Park, 1984).

In conclusion, in agreement with mechanical and electronic methods of assessing body shape and changes in volume on the induction of anaesthesia, stereophotogrammetry showed that there was no consistent change in body volume following the injection of thiopentone. Therefore, the decrease in FRC of 15–30% that is known to occur on induction does not seem to result from a volume change within the lung that is transmitted to the body surface in a consistent manner, if at all. The volume change of the "ribcage" was more predictable than that of the "abdomen" or the transitional section between the two, such that in those patients who were less than their expected weight the ribcage volume tended to increase, and in those heavier than their expected weight the ribcage volume tended to decrease. The changes in volume in both the ribcage and abdomen received a greater component from antero–posterior rather than lateral dimensional changes. Further research is required to determine the cause of the increase in body volume that occurs in some patients in spite of a probable decrease in FRC.

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CARDIOVASCULAR AND CATECHOLAMINE RESPONSES TO LARYNGOSCOPY WITH AND WITHOUT TRACHEAL INTUBATION

A. J. SHRIBMAN, G. SMITH AND K. J. ACHOLA

SUMMARY

The catecholamine and cardiovascular responses to laryngoscopy alone have been compared with those following laryngoscopy and intubation in 24 patients allocated randomly to each group. Following induction with fentanyl and thiopentone, atracurium was administered and artificial ventilation undertaken via a face mask for 2 min with 67% nitrous oxide in oxygen. Following laryngoscopy, the vocal cords were visualized for 10 s. In one group of patients, ventilation was then re-instituted via a face mask, while in the second group the trachea was intubated during the 10-s period and ventilation of the lungs maintained. Arterial pressure, heart rate and plasma noradrenaline and adrenaline concentrations were measured before and after induction and at 1, 3 and 5 min after laryngoscopy. There were significant and similar increases in arterial pressure and circulating catecholamine concentrations following laryngoscopy with or without intubation. Intubation, however, was associated with significant increases in heart rate which did not occur in the laryngoscopy-only group.

Since King and colleagues (1951) first described the reflex circulatory responses to direct laryngoscopy and tracheal intubation, there have been numerous publications concerning both the response and the manoeuvres by which it may be attenuated (Prys-Roberts et al., 1971; Derbyshire and Smith 1984). The majority of studies treat laryngoscopy and intubation as a single stimulus, which manifestly they are not. Although many anaesthetists believe that laryngoscopy is the major stimulus, the authors are unaware of any study that has specifically examined this question.

Recent work has correlated the cardiovascular and sympathoadrenal responses to laryngoscopy and intubation (Russell et al., 1981; Derbyshire et al., 1983). The present study was, therefore, designed to compare the cardiovascular and sympathoadrenal responses either to laryngoscopy alone or to laryngoscopy with intubation.

PATIENTS AND METHODS

Twenty-four adult patients (ASA grades I or II) undergoing elective surgery under anaesthesia requiring tracheal intubation gave their informed consent for the study, which was approved by the District Ethical Committee. Patients with a history of acid reflux or those whose body weight exceeded 15% of predicted values were excluded from the trial. The patients were allocated randomly to two groups comprising laryngoscopy with, or without, intubation of the trachea.

Premedication comprised diazepam 10 mg orally 1–2 h before operation. In the anaesthetic room a 16-gauge cannula was placed in a vein in the antecubital fossa after local intradermal injection of 0.5% plain lignocaine. A Dinamap cuff was placed on the contralateral arm, and ECG electrodes attached to record standard limb lead II. After a stabilization period of 5 min, control readings of arterial pressure (Dinamap) and heart rate (ECG) were noted, and 10 ml of blood withdrawn from the cannula for the measurement

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of plasma adrenaline and noradrenaline concentrations.

Induction of anaesthesia was achieved with fentanyl 0.1 mg followed, after 2 min, by a dose of thiopentone (3–4 mg kg^{-1}) sufficient to induce sleep, given over 60 s, and followed by atracurium 0.5 mg kg^{-1}. A Guedel type pharyngeal airway was inserted and the patient's lungs were ventilated with 67% nitrous oxide in oxygen via a face mask attached to a Bain breathing system receiving a fresh gas flow of approximately 90 ml kg^{-1}.

Ventilation and fresh gas flows were adjusted to maintain the end-expired carbon dioxide at a concentration of 5–5.5%, as measured by a Gould Capnograph using a sampling catheter placed under the mask.

Two minutes after the administration of atracurium, the arterial pressure and heart rate were recorded and a further venous sample obtained.

Immediately following sampling, the airway was removed and laryngoscopy performed using a Macintosh blade, enabling a clear view of the vocal cords for a 10-s period. For patients in the laryngoscopy-only group, the laryngoscope was then removed, the airway replaced and ventilation of the lungs recommenced via the face mask. For patients in the laryngoscopy and intubation group, the trachea was intubated during the 10-s period after which the airway was replaced and ventilation continued. Male patients received a 9.0-mm and female patients an 8.0-mm cuffed disposable tracheal tube.

Subsequently, in both groups the lungs were ventilated for a further 5 min and the end-tidal carbon dioxide concentration maintained at 5–5.5%. Venous blood samples were obtained and measurements of arterial pressure and heart rate were recorded at 1, 3 and 5 min after laryngoscopy. At the end of the study period in the laryngoscopy-only group, the patient's trachea was intubated and anaesthesia continued in the usual manner.

The 10-ml blood samples were collected into heparinized tubes and centrifuged as soon as possible. The separated plasma was analysed for noradrenaline and adrenaline concentrations using a high pressure liquid chromatographic technique, originally described by Hallman and colleagues (1978), which has been adapted in our laboratory (Fell, Achola and Smith, 1982; Derbyshire et al., 1983).

Data were analysed using paired and unpaired Student's t tests as appropriate.

RESULTS

The two groups were similar in respect of age, weight and sex (table I).

There were no significant differences between the groups in respect of arterial pressure at any time during the study (fig. 1). Following induction, systolic arterial pressure decreased significantly in both groups ($P < 0.01$) and following laryngoscopy with or without intubation, the systolic pressure increased significantly ($P < 0.001$) to values similar to those obtained before induction.

The diastolic arterial pressure also decreased in both groups after induction, but the changes were not significant. After laryngoscopy, diastolic arterial pressures increased significantly by 24% (laryngoscopy-only) and 36% (laryngoscopy and intubation) ($P < 0.001$, both groups) to values significantly greater than the pre-induction values (laryngoscopy, $P < 0.05$; laryngoscopy and intubation, $P < 0.001$). In both groups, diastolic arterial pressure decreased gradually over the next 5 min to values similar to those noted before induction.

Mean heart rates were similar before induction (fig. 2) and although there was a slight increase after induction, this was not significant. Laryngoscopy alone caused a small non-significant increase in mean heart rate, but in the laryngoscopy and intubation group there was a significant increase ($P < 0.001$) of 19%. Heart rates in both groups decreased gradually over the next 5 min, but they remained significantly different from each other for the whole period ($P < 0.01$). At 5 min after laryngoscopy alone, heart rate was significantly lower than that before induction ($P < 0.05$).

There were similar and significant increases in both plasma noradrenaline and adrenaline concentrations at 1 min following laryngoscopy with or without intubation ($P < 0.001$) (figs 3, 4). Noradrenaline concentrations remained significantly increased at 3 min after laryngoscopy in both groups.

TABLE I. *Details of patients (mean (SEM))*

Group	Age (yr)	Wt (kg)	Sex
Laryngoscopy-only	42.3 (4.5)	68.7 (3.9)	9M:3F
Laryngoscopy and intubation	45.3 (3.8)	68.1 (3.5)	8M:4F

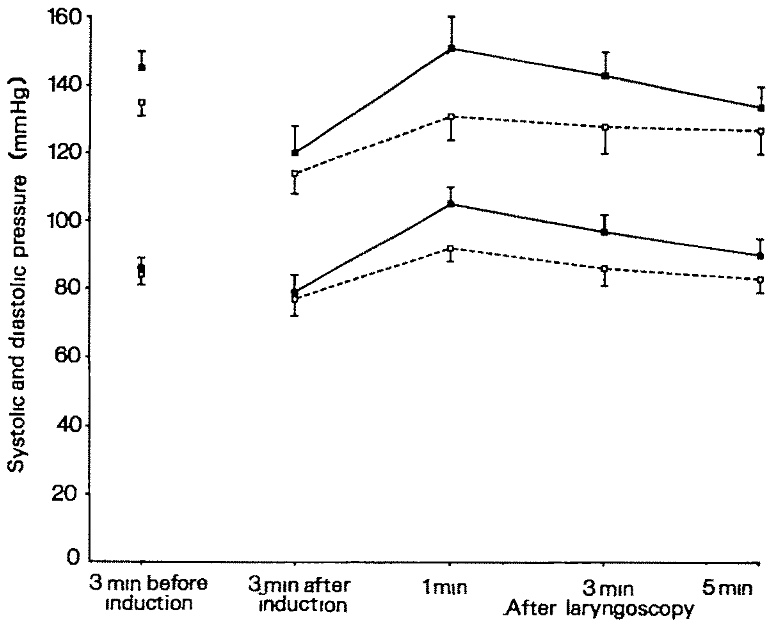

FIG. 1. Systolic and diastolic arterial pressures (mean ± SEM) in both groups before induction, and for the 5-min period after laryngoscopy. □- -□ = Laryngoscopy only ($n = 12$); ■——■ = laryngoscopy and intubation ($n = 12$).

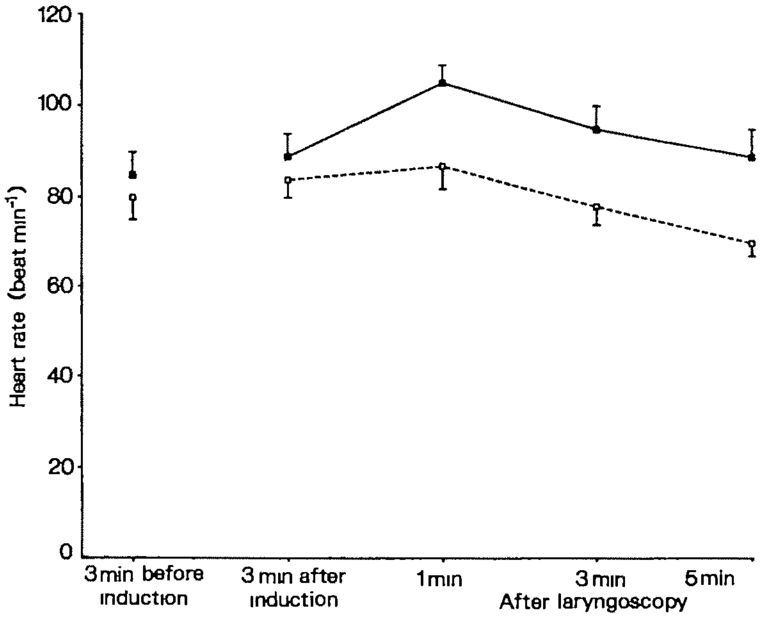

FIG. 2. Heart rates (mean ± SEM) in both groups before induction and for the 5-min period after laryngoscopy. □--□ = Laryngoscopy only ($n = 12$); ■——■ = laryngoscopy and intubation ($n = 12$).

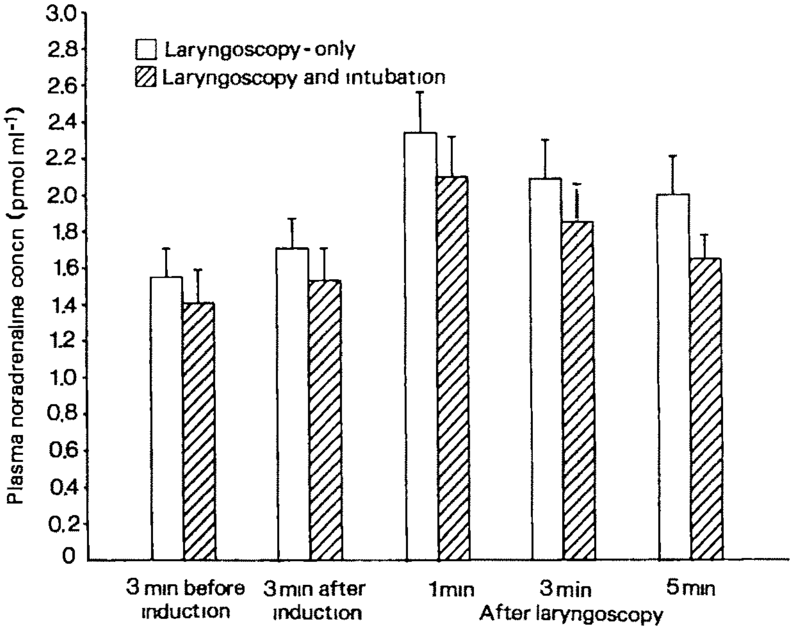

FIG. 3. Plasma noradrenaline concentrations (mean ± SEM) in both groups at each stage of the study. $n = 12$ (both groups).

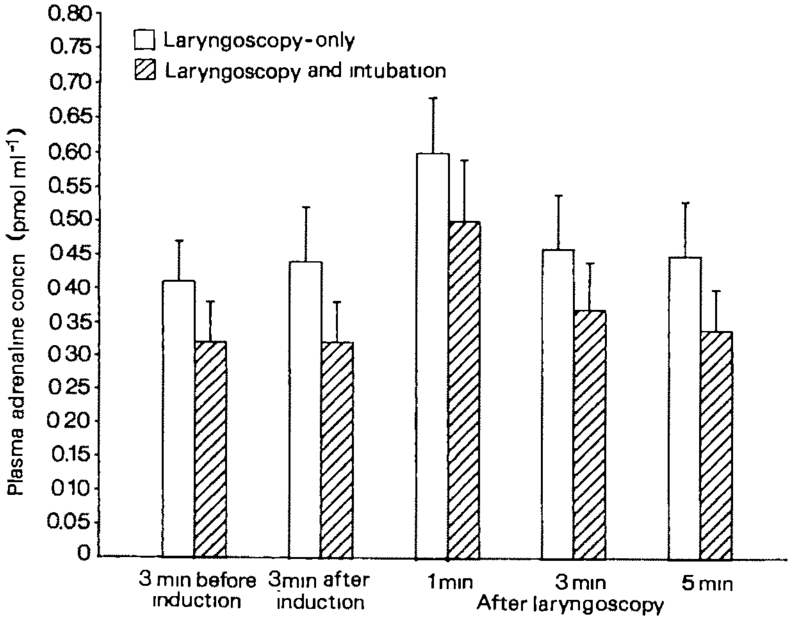

FIG. 4. Plasma adrenaline concentrations (mean ± SEM) in both groups at each stage of the study. $n = 12$ (both groups).

DISCUSSION

This study has shown that laryngoscopy alone generates the same pressor response and sympathoadrenal responses (in terms of circulating catecholamine concentrations) as laryngoscopy followed by intubation. This suggests that the major cause of the sympathoadrenal response to tracheal intubation arises from stimulation of the supraglottic region by tissue tension induced by laryngoscopy and that the placing of a tube through the cords and inflating a cuff in the infraglottic region contributes very little additional stimulation.

Laryngoscopy with intubation, however, was associated with significant increases in heart rate which were not apparent in the laryngoscopy-only group. This is difficult to explain, but implies that laryngoscopy produced a balanced stimulation of vagal and cardiac accelerator fibres, whereas intubation produced less vagal stimulation. The lack of vagolytic properties of the induction agents used in the study may have exaggerated any vagal stimulatory effect of the laryngoscopy.

Tomori and Widdicombe (1969) have shown that, in the paralysed cat, nervous activity in cervical sympathetic efferent fibres was significantly increased by stimulation of the epipharynx and laryngopharynx only, which also caused the greatest increase in mean arterial pressure. Stimulation of the tracheobronchial tree did not produce a significant increase in the activity of these fibres and caused only a small increase in mean arterial pressure.

Although Prys-Roberts and colleagues (1971) noted that tachycardia and hypertension occurred well before the act of intubation in treated and untreated hypertensives, data from only a single patient were presented to support this observation and, surprisingly perhaps, this observation does not seem to have initiated further studies to differentiate the contribution to sympathoadrenal activity of laryngoscopy from that of tracheal intubation. Stoelting (1977), however, did demonstrate changes in cardiovascular variables after laryngoscopy before intubation. Instead, subsequent studies have concentrated on the investigation of different methods of attenuating the sympathoadrenal responses induced by the combined act of laryngoscopy and tracheal intubation. This aspect of clinical investigation has been summarized elsewhere (Derbyshire and Smith, 1984).

The association between increased plasma catecholamine concentrations and pressor responses to tracheal intubation has been discussed by Derbyshire and Smith (1984). The present study has confirmed the work of Russell and colleagues (1981) and Derbyshire and colleagues (1983) showing that changes in plasma noradrenaline concentrations are linked with changes in mean arterial pressure. The association between changes in plasma adrenaline concentration and heart rate are less certain; in the present study there was a significant increase in plasma adrenaline concentration in both groups, but an increase in heart rate in only the laryngoscopy plus intubation group. In neither the study of Russell and colleagues (1981) nor that of Derbyshire and co-workers (1983) was there a significant correlation between plasma adrenaline concentration and heart rate or pulse pressure.

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Br. J. Anaesth. (1987), 59, 300–304

EFFECT OF TOPICAL LIGNOCAINE ON THE SYMPATHODRENAL RESPONSES TO TRACHEAL INTUBATION

D. R. DERBYSHIRE, G. SMITH AND K. J. ACHOLA

Hypertension and tachycardia associated with laryngoscopy and tracheal intubation are well recognized, and a good correlation has been demonstrated between the pressor response and changes in plasma catecholamine concentrations (Russell et al., 1981; Derbyshire et al., 1983). Lignocaine applied topically to the oropharynx has been shown to ameliorate the pressor response to laryngoscopy when given 5–10 min in advance of the manoeuvre and lignocaine, applied intratracheally immediately before intubation, has been shown to reduce the additional pressor component which accompanied the insertion of the tracheal tube (Denlinger, Ellison and Ominsky, 1974; Stoelting, 1977). However, in both of these studies, the technique of induction of anaesthesia with tracheal intubation did not emulate conventional clinical practice. Furthermore, no measurements were recorded of the changes in plasma catecholamine concentrations—observations which might be helpful in determining whether or not any beneficial effect of lignocaine results from the surface analgesia or systemic absorption.

The object of the present study was to compare the changes in cardiovascular variables and catecholamine concentrations which were associated with a conventional technique of induction of anaesthesia and tracheal intubation—with and without the application of topical lignocaine to the mucosa of the upper airway. At the same time, the opportunity was taken to examine the efficiency of delivery of lignocaine from a commercially available spray, the Laryng-o-jet.

SUMMARY

The catecholamine and cardiovascular responses to laryngoscopy and tracheal intubation have been studied in 30 patients undergoing elective gynaecological surgery, allocated randomly to one of three groups: group 1 received 4% lignocaine 160 mg using a Forrester Spray; group 2 received 4% lignocaine 160 mg by "Laryng-o-jet"; group 3 received an equal volume of saline administered by Forrester Spray. In all three groups, there were similar and statistically significant increases in mean arterial pressure and plasma adrenaline and noradrenaline concentrations 1 min after intubation, with diminution of these responses by 5 min after intubation. There were no differences between the three groups at any stage, which suggests that topical anaesthesia of the mucosa of the upper airway, as performed conventionally, is ineffective as a means of ameliorating the pressor and catecholamine responses to routine laryngoscopy and intubation.

PATIENTS AND METHODS

Thirty otherwise healthy women about to undergo elective gynaecological surgery for which tracheal intubation would normally be used, gave informed consent for the study, which was approved by the District Ethical Committee. The patients were randomly allocated to one of three groups. Group 1 received topical laryngeal and tracheal lignocaine (160 mg as 4%) delivered from a conventional Forrester spray: group 2 received 4% lignocaine 160 mg from a proprietary device (Laryng-o-Jet, International Medication Systems Ltd); group 3 (control group) received 0.9% sodium chloride 4 ml to the larynx and trachea delivered from a Forrester spray.

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Premedication comprised lorazepam 2 mg and metoclopramide 10 mg administered 90 min before anaesthesia. In the anaesthetic room a large vein in the antecubital fossa was cannulated under local analgesia and, after several minutes, a sample of venous blood (10 ml) was taken to permit measurement of plasma catecholamine concentrations. Systemic arterial pressure and heart rate were measured (Dinamap 845). Anaesthesia was induced with papaveretum 10 mg and 2.5% thiopentone 3–5 mg kg^{-1}. Atracurium 0.5–0.6 mg kg^{-1} was administered to provide neuromuscular blockade. Anaesthesia was maintained subsequently with 67% nitrous oxide in oxygen supplemented with 0.2% enflurane administered through a Bain breathing system delivering 70–80 ml kg^{-1} fresh gas flow. One minute after induction (assessed by loss of eyelash reflex), a further sample of venous blood was obtained, and heart rate and arterial pressure determined. Immediately afterwards, laryngoscopy was performed using a Macintosh blade and the predetermined spray was applied to the larynx, trachea and laryngopharynx. The laryngoscope was then withdrawn; 1 min later laryngoscopy and tracheal intubation were performed, and 1 and 5 min after intubation further samples of blood, and measurements of arterial pressure and heart rate, were obtained. Surgery then proceeded normally.

Venous blood samples for the measurement of plasma catecholamine concentrations were handled differently from our usual practice (Derbyshire et al., 1983). All samples were collected into lithium heparin tubes and plasma was separated at 4000 rev min^{-1} within 15 min. The supernatant was stored at 4 °C for up to 3 h before being frozen at less than −18 °C before transfer to Leicester, where storage was maintained at −70 °C until analysis using high pressure liquid

TABLE I. *Patient data (mean ± SEM)*

Group	Age (yr)	Weight (kg)	Thiopentone (mg kg^{-1})	Atracurium (mg kg^{-1})
Forrester + LA (n = 10)	35(4)	63(2)	4.4(0.2)	0.5
Laryng-o-Jet (n = 10)	35(3)	60(2)	4.8(0.2)	0.5
Forrester + saline (n = 10)	38(3)	59(2)	5 (0.2)	0.48

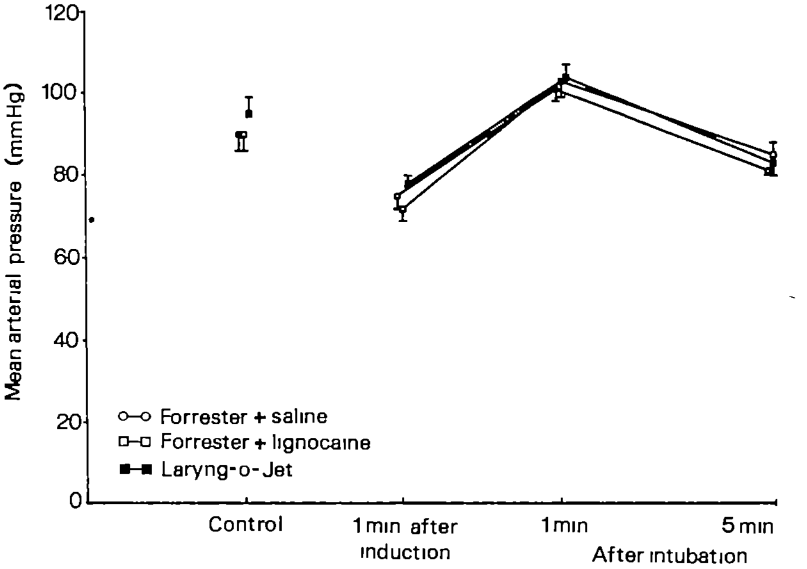

FIG. 1. Mean arterial pressures (mean ± SEM) in the three groups. n = 10 in each group.

chromatography with electrochemical detection as described in our previous publication (Derbyshire et al., 1983).

Data were analysed using paired and unpaired Student's *t* tests, as appropriate.

RESULTS

There were no significant differences between the groups in respect of age, weight or doses of drugs used at the induction of anaesthesia (table I).

Following the induction of anaesthesia, there were similar and significant decreases in mean arterial pressure in all three groups (20%, 17% and 18% in groups 1, 2 and 3, respectively) (fig. 1). Heart rates were increased by 25, 9, and 13%, in the three groups respectively (table II).

One minute after tracheal intubation, there were comparable and sigificant increases in mean arterial pressure (43%, 33% and 35% in groups 1, 2 and 3, respectively). Heart rates increased significantly over control values by 35, 17 and 18% after intubation. Five minutes after intubation, mean arterial pressures and heart rates were similar to their control values.

These cardiovascular changes were accompanied by similar changes in plasma catecholamine concentrations (figs 2 and 3). Following tracheal intubation, there were increases of 43%, 50% and 44% (groups 1, 2 and 3) in plasma noradrenaline concentrations, and 100%, 75% and 40% (ns) increases in plasma adrenaline concentrations in groups 1, 2 and 3, respectively.

There were no significant differences between the three groups in arterial pressures, heart rates or plasma catecholamine concentrations at any period of the study.

TABLE II. *Change in heart rate in three groups of patients (mean ± SEM)*

	Control	After induc. 1 min	After intubation 1 min	After intubation 5 min
Forrester + LA (n = 10)	79.3±2.65	98.9±6.2	107.0±5.7	85.3±4.7
Laryng-o-jet (n = 10)	85.2±2.4	95.9±3.8	100.1±3.9	79.5±3.6
Forrester + saline (n = 10)	88.9±4.4	96.7±4.6	105.1±4.2	86.2±3.7

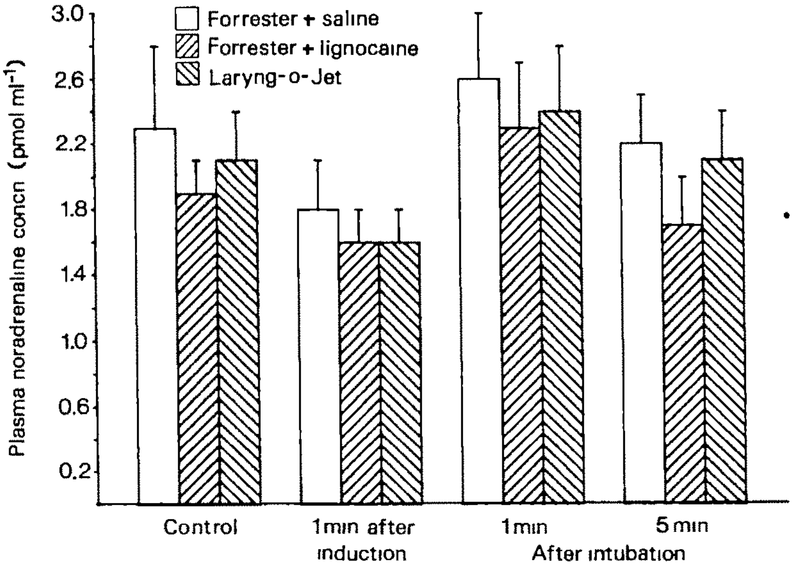

FIG. 2. Plasma noradrenaline concentrations (mean ± SEM) in the three groups. n = 10 in each group

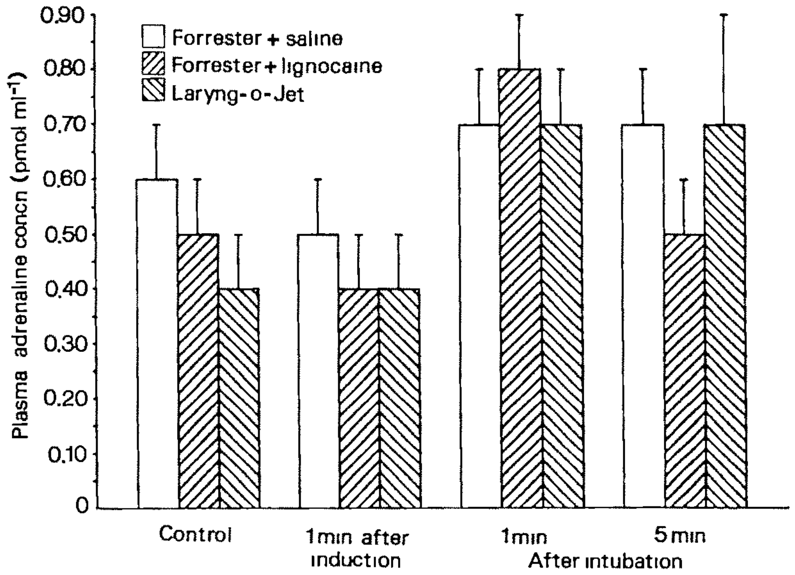

FIG. 3. Plasma adrenaline concentrations (mean ± SEM) in the three groups. $n = 10$ in each group.

DISCUSSION

This study has failed to demonstrate that the prior application of topical analgesia with lignocaine to the upper airway immediately before intubation of the trachea modifies the subsequent pressor or sympathoadrenal responses. In this respect, the findings would appear to be at variance with the study of Denlinger, Ellison and Ominsky (1974) and that of Stoelting (1977). However, there are important differences between the design of these studies and the present ones.

In the study by Denlinger, Ellison and Ominsky (1974), the design of the investigation was as follows: in patients undergoing cardiac surgery, anaesthetized with morphine 1 mg kg^{-1} and nitrous oxide in oxygen, tubocurarine and suxamethonium, an initial laryngoscopy and tracheal spray with lignocaine was accompanied by a smaller increase in arterial pressure 1–5 min afterwards than occurred in a second group of patients in whom saline was used in place of lignocaine. Five minutes later, laryngoscopy and intubation were performed and in the saline-treated group the increase in pressure was greatly exaggerated, whilst the increase in pressure in the lignocaine-treated group was the same as that following the initial laryngoscopy and tracheal spray. This suggests that tracheal intubation is accompanied by sympathoadrenal stimulation additional to that of laryngoscopy alone, and that this additional stimulus may be blocked by intra-tracheal spray with lignocaine 120 mg 70 kg^{-1}, allowing 5 min for surface analgesia to take effect. The difference in response between the two groups following the initial laryngoscopy can be accounted for only on the grounds that the two groups of patients were not drawn from the same population or that absorption of lignocaine occurred, resulting in subsequent myocardial depression.

Stoelting (1977) investigated several aspects of this topic in patients premedicated with morphine 8–15 mg and hyoscine 0.4 mg and anaesthetized with thiamylal 4 mg kg^{-1}. Suxamethonium 2 mg kg^{-1} and tubocurarine 40 µg kg^{-1} were administered also. By varying the duration of laryngoscopy, it was shown that the pressure response increased progressively over 45 s of continuous stimulation and that a further 15 s of laryngoscopy caused little additional stimulation. In addition, it was shown that oropharyngeal gargling with lignocaine 500 mg 10 min before the induction of anaesthesia was almost equally as effective as lignocaine 1.5 mg kg^{-1} given i.v. 90 s before laryngoscopy. In patients given laryngeal spray with lignocaine 2 mg kg^{-1}, there was no further significant increase in pressure when tracheal intubation was performed after 60 s of laryngoscopy, although there was a significant increase in the group given lignocaine i.v.

This suggests that the response to laryngoscopy is dependent on the duration of laryngoscopy, reaching a maximum at approximately 45 s, and that tracheal intubation offers a further additional stimulation. The response of the former may be attenuated, but not abolished, by the oropharyngeal administration of lignocaine—although it is not possible to exclude, in this study, an effect from the systemic absorption of lignocaine. In addition, it suggests that the immediate tracheal application of lignocaine should attenuate the pressor response resulting from the placement of the tracheal tube.

The investigation reported in the accompanying paper (Shribman, Smith and Achola, 1987) also suggests that most of the sympathoadrenal response to tracheal intubation results from laryngoscopy alone. However, the anaesthetic technique differed slightly from that used in the present investigation.

It is possible to interpret the negative findings of the present study on the following grounds. Application of topical lignocaine would be expected to affect only the additional stimulation resulting from intubation of the trachea, which would be expected to be extremely small in the present study in relationship to that produced by laryngoscopy (Shribman, Smith and Achola, 1987). In addition, the use of enflurane in the maintenance of anaesthesia could result in suppression of any potential additional small stimulus from intubation.

The anaesthetic sequence used here was one which might be used in everyday clinical practice. It is a popular misconception that laryngotracheal lignocaine is beneficial: "The value...of lignocaine just before tracheal intubation was demonstrated by the minimal additional MAP increases..." (Stoelting, 1977). "The laryngeal reflex can be subdued if [local] analgesic solution is sprayed onto...the cords..." (Atkinson, Rushman and Lee, 1982). However, the present study suggests that, in terms of reducing the sympathoadrenal responses with conventional anaesthesia, the manoeuvre is ineffective in respect of laryngoscopy and intubation.

It has been shown previously that i.v. lignocaine reduces the pressor response to intubation (Stoelting, 1977; Hamill et al., 1981). It is likely that this amelioration occurs as a result of direct myocardial depression (Thomas, 1975; Ritchie and Green, 1980) or the deepening of anaesthesia. Furthermore, it is well known that topically applied lignocaine is absorbed systemically, but there is dispute on whether or not *peak* serum concentrations occur at 5 min (Pelton et al., 1970) or later (Chu et al., 1975) following application of topical lignocaine to the upper airway.

The Laryng-o-jet is a convenient device for the administration of topical lignocaine, for it allows more rapid administration. It might have been expected from the study of Stoelting (1977) that this reduction in the duration of laryngoscopy, when compared with the time required using the Forrester spray (filled twice), might have yielded benefit. Unfortunately, we did not measure "spray time", or the total duration of laryngoscopy, but there is no doubt that this was shortest in the Laryng-o-jet group. However, we did not demonstrate any advantage from the shorter duration of laryngoscopy, although this might be accounted for again by the different anaesthetic techniques used in the present study and that of Stoelting (1977).

In conclusion, we have failed to demonstrate any beneficial effect of spraying the cords and upper airway with 4% lignocaine in terms of the subsequent pressor response to intubation. Before this conclusion may be extrapolated elsewhere, care must be taken to define the technique of anaesthesia used and the duration of laryngoscopy.

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HAEMODYNAMIC EFFECTS OF VECURONIUM, PANCURONIUM AND ATRACURIUM IN PATIENTS WITH CORONARY ARTERY DISEASE

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SUMMARY

Thirty patients with ischaemic heart disease scheduled for coronary artery bypass grafting were randomly allocated to three equal groups. Following morphine, hyoscine and pentobarbitone premedication, anaesthesia was induced with diazepam 0.3 mg kg^{-1}. Five minutes later neuromuscular blockade was induced with pancuronium 0.1 mg kg^{-1}, vecuronium 0.1 mg^{-1} or atracurium 0.5 mg kg^{-1}, followed after 6 min by fentanyl 25 µg kg^{-1}. Pancuronium and atracurium caused significant increases in heart rate, while vecuronium induced little change. Systemic vascular resistance decreased significantly from 1515 dyn s cm^{-5} to 1200 dyn s cm^{-5} following atracurium. Cardiac index was increased transiently in the atracurium group, but a more sustained increase was observed following pancuronium. Nine patients in the atracurium group showed skin flushing and one developed skin weals.

Shortly after its introduction to anaesthetic practice, pancuronium was used to block neuromuscular transmission in poor risk patients, including those about to undergo cardiac surgery. Although not devoid of adverse haemodynamic effects (Kelman and Kennedy, 1971; Stoelting, 1972), pancuronium was advocated for patients undergoing coronary artery bypass grafting (Heinonen and Yvjola, 1980) and has been used widely during this operation (Stanley, Philbin and Coggins, 1979; Stanley et al., 1980; Quinton et al., 1981). The increase in heart rate produced by pancuronium has been considered acceptable in comparison with the histamine release (Comroe and Dripps, 1946; MacIntosh and Paton, 1949), ganglion blockade and tachycardia (Smith and Whitcher, 1967; Kennedy and Kelman, 1970) produced by some of its competitors.

In equipotent doses vecuronium and atracurium have similar durations of action which are shorter than that of pancuronium (Agoston et al., 1980; Marshall, Agoston et al., 1980; Payne and Hughes, 1981). While vecuronium depends, like pancuronium, on renal and hepatic mechanisms to terminate its action, atracurium is broken down spontaneously in the plasma by Hofmann elimination and ester hydrolysis. Both agents have been shown to provide a high degree of cardiovascular stability when studied in animals and man (Marshall, McGrath et al., 1980; Payne and Hughes, 1981; Philbin et al., 1983).

Therefore, we decided to compare the haemodynamic effects of atracurium and vecuronium with those of pancuronium in patients about to undergo aorto–coronary bypass grafting. Evidence of histamine release was sought in relation to the use of atracurium.

PATIENTS AND METHODS

With the approval of the local Ethical Committee, 30 adult patients scheduled for coronary artery bypass surgery (CABG) were studied. Patients with a left ventricular ejection fraction of less than 0.50, or with any hepatic, renal or neuromuscular

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disorder were excluded. The majority of the patients were receiving nitrates, propranolol and nifedipine during the 3 days before surgery and all drugs were discontinued after the dose at 22.00 h on the evening before surgery. Premedication consisted of pentobarbitone 100 mg by mouth 2 h before anaesthesia, and morphine 10 mg and hyoscine 0.2 mg i.m. 1 h later. Peripheral, jugular venous and radial arterial cannulations were performed under local anaesthesia, and an ECG monitor (Hewlett–Packard 78205C) attached before the induction of anaesthesia.

A triple-lumen thermodilution flotation catheter was passed into the pulmonary artery for the measurement of central venous (CVP), pulmonary artery (PAP) and pulmonary capillary wedge (PCWP) pressures. Cardiac output (CO) was determined (thermodilution) using iced injectate. All measurements were obtained in triplicate with less than 10% variation using a cardiac output computer (Edwards Laboratories 9520A).

Following the attachment of the monitoring devices a 15-min period was allowed for stabilization of the cardiovascular system, after which baseline measurements were obtained. Anaesthesia was then induced by the injection (over 10 s) of diazepam 0.3 mg kg^{-1}. (All drugs were injected to a freely-running infusion in the external jugular vein.) Patients received dextrose–saline solution 50–100 ml over the period of the study. Five minutes later, the eyelash reflex having been lost, neuromuscular blockade was produced by the i.v. injection over 5 s of approximately equipotent doses (Gramstad and Lilleaasen, 1982) of pancuronium (0.1 mg kg^{-1}), vecuronium (0.1 mg kg^{-1}) or atracurium (0.5 mg kg^{-1}), allocated to patients by use of a table of random numbers.

Eleven minutes after the induction of anaesthesia, fentanyl 25 μg kg^{-1} was given and tracheal intubation accomplished 1 min later. The degree of neuromuscular blockade was assessed with a train-of-four stimulus delivered to the ulnar nerve at the wrist, via surface electrodes, from a peripheral nerve stimulator (Myotest Biometer Limited). From the preanaesthetic period to the end of the study, the patients breathed oxygen via a non-rebreathing circuit, ventilation being assisted as required to maintain normocarbia. Surgery was not started before the end of the study period.

Cardiovascular measurements were recorded continuously (Hewlett–Packard Optical Recorder) for 25 min from time zero. Mean systemic, pulmonary and venous pressures were obtained by electronic integration of the haemodynamic wave forms. Cardiac output and arterial blood-gas tensions were measured at 0, 3, 6, 9, 15 and 20 min. The measurements were used to calculate cardiac index (CI), and systemic and pulmonary vascular resistances (SVR, PVR).

In assessing the effects of the individual neuromuscular blockers on cardiovascular variables in the time period after their administration, the results have been subjected to repeated measures analysis of variance. When drugs were compared, account was taken of differences in the variables at baselines by using the 3-min results as covariates in the analyses of variance.

In order not to obscure the small cardiovascular changes which might occur after the administration of the neuromuscular blockers by the much larger, and possibly more variable, changes resulting from the administration of fentanyl, two analyses were performed for each variable. The first included results in the 6–11 min period only, while the second included additionally the results obtained at 15 and 20 min.

Where statistically significant effects were observed in the analysis of variance, means were compared using the appropriate standard errors derived from the analysis of variance.

RESULTS

Details of the three groups of patients are summarized in tables I and II; these are broadly comparable with regard to weight, body surface area, age, sex and previous drug therapy.

All patients received diazepam 0.3 mg kg^{-1} for induction of anaesthesia at time 0, and in comparing the haemodynamic effects of the neuromuscular blocking drugs, values 3 min after induction have been regarded as the baseline. At this time one-way analysis of variance showed that there were no significant differences between the groups for any of the variables except PCWP ($P < 0.05$), which was greater in the atracurium group than in the other two groups.

The analyses of heart rates (HR) between 6 and 11 min showed evidence ($P < 0.025$) of a different effect between the drugs, but the heart rate in each group behaved in a similar manner with time (fig. 1). This suggests that there were differences in heart rate during this period between the three drugs after adjustment for baseline readings, and

TABLE I. *Physical characteristics of patients (mean ± SEM)*

Neuromuscular blocker	Body weight (kg)	Age (yr)	Body surface area (m^2)	Sex	
				Male	Female
Pancuronium	66.8 ± 5.82	61.0 ± 5.05	1.72 ± 0.11	7	3
Vecuronium	73.5 ± 6.39	53.6 ± 6.37	1.85 ± 0.10	8	2
Atracurium	70.0 ± 4.26	51.6 ± 5.79	1.77 ± 0.08	8	2

TABLE II. *Previous drug treatment of patients (10 in each group)*

Relaxant group	Number of patients receiving			
	Nitrates	Propranolol	Nifedipine	Digoxin
Pancuronium	9	6	8	2
Vecuronium	7	8	8	1
Atracurium	9	9	9	1

the differences were maintained throughout the period. Pancuronium and atracurium produced significant increases in the HR during this period compared with the 3-min baseline. Following the administration of fentanyl the decrease in HR at 15 and 20 min was significant compared with baseline in the patients receiving vecuronium ($P < 0.05$). Two patients in this group had heart rates less than 40 beat min^{-1}.

There were no significant differences at 6 and 9 min in intravascular pressures (table III) between the three groups after adjusting for differences at baseline. Following the administration of fentanyl there were marked decreases in MAP and PAP in all groups.

There was a significant interaction between the myoneural blockers and time for cardiac index ($P < 0.025$). This indicates a difference in the pattern of the changes in cardiac index over the 6-min period in the three groups. An increase in CI in the atracurium group at 6 min had returned to near baseline values by 9 min. In contrast, the increase in CI in the pancuronium group did not occur until 9 min. At both 6 and 9 min the CI following vecuronium had decreased slightly (ns) from the baseline readings.

Although the interaction between the neuromuscular blockers and time in the analysis of variance of SVR was not significant

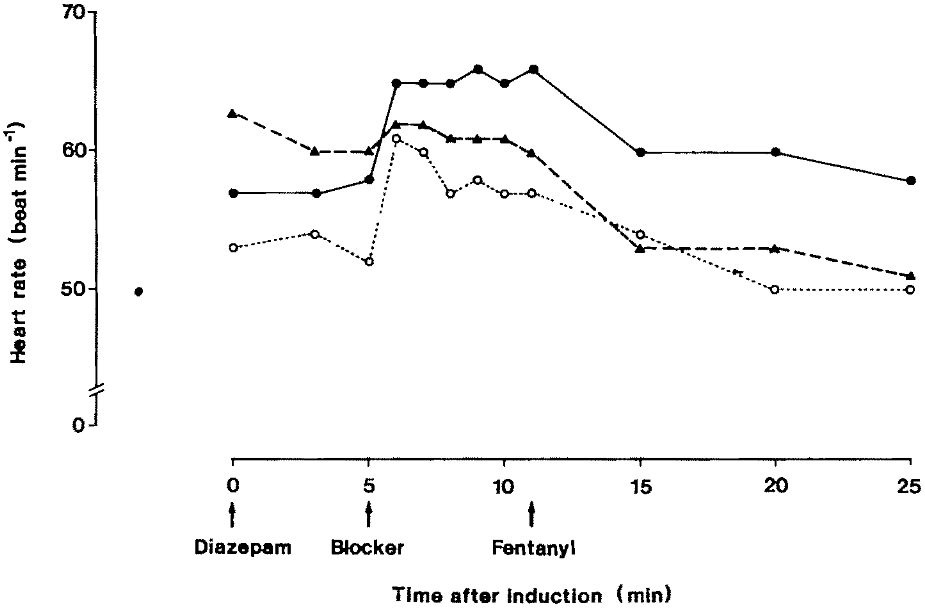

FIG. 1. Heart rates in the three groups of patients after induction of anaesthesia.
●—● = Pancuronium; ▲---▲ = vecuronium; ○ · · · ○ = atracurium.

TABLE III. *The principal cardiovascular measurements (mean ± SEM) in the three groups at various times after induction of anaesthesia with diazepam (0). The chosen neuromuscular blocker was given at minute 5 and the fentanyl at minute 11 after induction*

	Time (min) after induction					
	0	3	6	9	15	20
HR (beat min^{-1})						
Pancuronium	57±3.2	57±4.3	65±4.6	66±4.7	60±3.7	60±3.6
Vecuronium	63±4.3	60±3.0	62±3.8	61±2.2	53±3.4	53±3.2
Atracurium	53±3.0	54±3.4	61±3.4	58±4.6	54±4.3	50±4.0
MAP (mm Hg)						
PC	93±4.3	84±3.4	80±4.3	82±5.8	68±4.0	66±3.0
VC	106±6.0	89±3.8	84±4.3	85±5.1	69±4.3	73±3.3
AC	105±2.6	90±3.9	78±4.3	84±4.9	75±2.4	74±2.1
MPAP (mm Hg)						
PC	16.1±1.4	16.8±1.2	15.2±1.1	14.4±1.0	12.1±0.8	12.9±0.9
VC	18.1±1.2	15.7±1.0	15.8±1.2	15.0±0.8	13.3±0.7	13.0±0.7
AC	21.1±1.2	19.3±1.0	17.5±0.8	18.2±0.9	15.5±0.8	14.9±0.9
PCWP (mm Hg)						
PC	8.3±0.9	9.2±1.0	8.4±1.0	8.6±0.8	7.1±0.7	6.6±0.6
VC	9.5±1.2	9.1±1.2	9.5±1.2	9.0±0.7	7.9±0.8	8.2±0.8
AC	13.3±1.0	12.4±0.6	11.7±0.7	12.0±0.6	10.1±0.5	9.4±0.6
CI (litre min^{-1} m^{-2})						
PC	2.57±0.19	2.30±0.13	2.35±0.13	2.54±0.17	2.35±0.19	2.31±0.19
VC	2.75±0.2	2.41±0.12	2.32±0.16	2.27±0.12	2.15±0.11	2.03±0.10
AC	2.56±0.11	2.40±0.12	2.67±0.21	2.46±0.18	2.33±0.15	2.17±0.11
SVR (dyne s cm^{-5})						
PC	1666±178	1632±157	1517±137	1449±136	1280±115	1287±106
VC	1671±177	1573±150	1524±138	1561±152	1334±126	1469±84
AC	1702±55	1525±55	1200±67	1416±93	1335±53	1409±57
PVR (dyne s cm^{-5})						
PC	154±31	147±24	131±16	112±23	100±19	131±17
VC	146±19	123±15	123±15	119±14	112±13	104±11
AC	140±16	133±16	101±13	118±20	104±12	114±10

$(0.05 < P < 0.1)$, examination of the mean at 6 min showed a highly significant decrease in the atracurium group $(P < 0.001)$. Other derived variables showed no significant changes between the groups or within each group until after the administration of fentanyl.

Nine out of 10 patients in the atracurium group developed skin flushes of varying degrees of severity immediately after receiving the drug, with one patient also developing large skin weals (0.5–1.0 cm diameter) widely distributed over his body. No patients showed any signs of bronchospasm and the skin changes faded spontaneously within 20 min of their appearance. No evidence of any skin or systemic changes suggestive of histamine release was seen in either the vecuronium or pancuronium groups.

DISCUSSION

The cardiovascular effects of pancuronium are well recognized: it has been shown to induce small increases in HR, CO and MAP (Kelman and Kennedy, 1971; Lyons and Clarke, 1972), but these have been regarded as at worst acceptable or at best a positive advantage, countering any tendency for these variables to decrease as anaesthesia is induced. The causes of these effects are thought to be a combination of post-ganglionic vagal blockade (Saxena and Bonta, 1970) and the blocking of noradrenaline re-uptake (Domenech et al., 1976). Although the changes in HR seen with pancuronium may be marked in certain patients, the lack of histamine release and of ganglionic blockade have ensured its popularity in cardiovascular anaesthesia. Despite this, the combination of pancuronium and metocurine has been advocated to minimize the changes in HR (McDonald and Zaidan, 1984). Fentanyl–pancuronium anaesthesia has also been advocated for patients undergoing CABG because of the lack of neuroendocrine stress response and subsequent haemodynamic stability (Stanley, Philbin and Coggins, 1979; Stanley et al., 1980; Quinton et al., 1981). Other investigators have reported adverse haemodynamic changes (Edde, 1981; Waller et al., 1981) and evidence of intraoperative myocardial ischaemia (Sonntag et al., 1982; Thompson, Mutch and Culligan, 1984).

The present findings confirm that pancuronium tends to cause a moderate increase in HR with a small increase in CI which returns to pre-relaxant values upon the administration of fentanyl. By not inducing such an increase in HR, vecuronium, as anaesthesia deepens, allows the CI to decrease, although this did not attain statistical significance.

In a comparison of a variety of non-depolarizing neuromuscular blockers, Marshall, McGrath and colleagues (1980) and Booij and colleagues (1980) reported no significant cardiovascular changes with vecuronium, in contrast to the significant increases in HR, MAP, PCWP and CI found with pancuronium. Using vecuronium in a patient group similar to those in the present study, Morris and colleagues (1983) showed no significant changes in HR, MAP and PCWP, but a small though significant increase in CO, and decrease in SVR. However, they used a larger dose of the drug (0.28 mg kg^{-1}) and this may explain the differences between their results and those reported here. Allowing for the differences in dose and the fact that only five of seven patients were receiving beta-blocking drugs, the results of both studies are in broad agreement and support the conclusion that vecuronium has little effect on the cardiovascular system and is better than pancuronium at maintaining cardiovascular stability.

The lack of any chronotropic effect with vecuronium may allow the HR to decrease to unacceptably low values. This situation is more likely to be encountered in patients who are clinically adequately controlled on beta-blocking drugs such as is commonly the case in coronary artery surgery (Sill et al., 1984). The deep levels of anaesthesia produced by the high-dose fentanyl technique have been shown to block the stimulating effects of tracheal intubation (Bennett and Stanley, 1980). Such profound anaesthesia in beta-blocked patients coupled with the use of vecuronium probably requires a higher level of vigilance by the anaesthetist than when the heart rate is supported by the administration of pancuronium. This difficulty was foreseen by Savarese and Kitz (1973), who suggested that the relative bradycardia and hypotension caused by most modern anaesthetic techniques may make drugs with a mild vagal blocking effect more acceptable than a drug with a complete lack of cardiovascular effects. It remains to be seen whether the advantages shown by vecuronium plus any decrease in myocardial oxygen consumption which the drug may offer, will be sufficient to overcome the problems of marked bradycardia in certain patients in clinical practice. These findings are supported by the study of Salmenperä and colleagues (1983) who observed a significant decrease in HR and CO following vecuronium administered to patients anaesthetized with high-dose fentanyl. Despite the risk of atrioventricular dissociation or slow heart rate, they suggested that patients with limited coronary vascular reserve may benefit from the negative chronotropic effect of vecuronium.

Vecuronium bromide is supplied as a freeze-dried powder to be freshly dissolved before use. Atracurium besylate must be stored at between 2 and 5 °C to avoid spontaneous decomposition by Hofmann elimination. These requirements were adhered to during this study, atracurium besylate being injected to a continuously running infusion to an external jugular vein within 15 min of its removal from the refrigerator. The changes seen in the atracurium group suggest histamine release to a greater degree than has been seen in previous clinical studies with the drug (Hilgenberg, Stoelting and Harris, 1983). Basta and co-workers (1983) have shown that atracurium produces a two-fold increase in serum histamine concentration when given in a dose of 0.6 mg kg^{-1}, while vecuronium, in a dose of 0.2 mg kg^{-1}, induces no increase in histamine concentration. The decreases in MAP and SVR with the accompanying transient increases in HR and CI are suggestive of the release of histamine or other vasoactive substance. Sokoll and co-workers (1983) studying the haemodynamic effects of atracurium in patients undergoing nitrous oxide–enflurane anaesthesia, found no indication of histamine release and no untoward side effects on cardiovascular performance. Philbin and co-workers (1983), studied the effects of atracurium in patients undergoing coronary artery surgery and found significant decreases in MAP, but no change in CO or SVR. However, these results excluded one patient who, having received 0.3 mg kg^{-1} of the drug exhibited a "typical histamine response" with large increases in CO and a decrease in MAP.

The questions raised by the reported effects of atracurium in this and previous studies may decrease the use of the drug in patients in whom a high degree of haemodynamic stability is essential. However, tubocurarine is well known to produce more marked histamine release and, despite this, has remained popular in clinical practice for 40 years while not offering any of the advantages of lack of ganglionic blockade or short duration of action seen with atracurium.

Vecuronium, with its shorter duration of action and lack of cardiovascular stimulation, offers significant advantages over pancuronium. The wide margin of safety between the clinical dose and that producing significant cardiovascular side effects, allows the initial dose of the drug to be increased to give a duration of action comparable to that of pancuronium, should this be desired, without any tendency to develop side effects. Although the idea of a neuromuscular blocking drug without cardiovascular side effects is attractive, its use may result in heart rates that are slower than many anaesthetists consider acceptable.

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CAN ONE RISK FASTING THE OBSTETRIC PATIENT FOR LESS THAN 4 HOURS?

M. LEWIS AND J. S. CRAWFORD

SUMMARY

Forty patients scheduled for elective Caesarean section under general anaesthesia were divided into two groups. A control group of 20 patients was treated conventionally, whereas the other group was offered a light breakfast of tea and toast within 4 h of surgery. The volume of gastric contents was significantly greater ($P \leqslant 0.02$) *and the pH of the aspirate significantly lower* ($P \leqslant 0.05$) *in the study group than in the control group. It is, therefore, not recommended that obstetric patients be fasted for less than 4 h.*

It is routine practice in this hospital to fast overnight patients scheduled to undergo elective lower segment Caesarean section, having offered them a snack of tea and toast at about 22.00 h that evening. In the light of an article (Miller, Wishart and Nimmo, 1983) which concluded that it was unnecessary to fast patients for elective gynaecological surgery for more than 4 h, we decided to undertake a similar study in patients undergoing elective Caesarean section—obstetric patients having been specifically excluded from the study by Miller and colleagues.

PATIENTS AND METHODS

Forty patients scheduled for elective lower segment Casesarean section were admitted to the study, which had been approved by the local Ethical Committee. Patients gave informed consent and were divided into two groups. The control group (20 patients) were fasted overnight and received Mist. Magnesium Trisilicate B.P.C. (MMT) 20 ml on leaving the ward, and a further 20 ml if anaesthesia was not induced within 15 min of their receiving the first dose. The other group were offered a breakfast of tea and toast at the normal time; all 20 elected to drink a cup of tea, but only 11 chose to eat the toast. The MMT regimen was exactly the same as in the control group. The times at which breakfast and MMT were given were noted, as was the time at which anaesthesia was induced.

A standard technique was used. Thiopentone 5 mg kg^{-1} and suxamethonium 100 mg were given i.v. after pre-oxygenation for 3 min and the application of cricoid pressure. The trachea was intubated and the lungs ventilated with oxygen–nitrous oxide (ratio 2:1) and 0.5% halothane. Flow rates were adjusted to obtain an end-tidal P_{CO_2} of 4.0 kPa as verified by a Datex-Normocap end-tidal carbon dioxide monitor. Neuromuscular blockade was maintained with pancuronium 4–5 mg. The nitrous oxide:oxygen ratio was reversed after the delivery of the baby and fentanyl 200 μg was given. At this point an 18-gauge Salem sump tube was passed into the stomach (through the mouth) in the control group, or a 36-French gauge large-bore plastic tube in the fed group. A 36-French gauge tube was used in the fed group in order to maximize the amount of aspirate obtained. Since the aspirate in the control group should only be of a liquid nature as a result of the period of fasting, it was thought that passage of a non-traumatic 18-gauge Salem sump tube was justified. The time of the first aspirate was noted and the pH of this sample was measured using a Corning Digital pH meter PT 1–15. At the end of the procedure, and before the antagonism of neuromuscular blockade with neostigmine 5 mg (plus atropine 1.2 mg), the patients were turned from side to side and the total aspirate obtained noted. MMT 20 ml was inserted via the gastric tube before it was removed.

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TABLE I. *Intervals, volumes and pH measured (mean values (SD)). *Although nine patients received tea, no stomach aspirate was obtainable from one*

	Interval MMT to induction (min)	Final dose MMT to aspiration (min)	Interval b'fast to induction (min)	Interval b'fast to aspiration (min)	Volume aspirated (ml)	pH
Control	8.3	34.4	—	—	33.2	8.24
($n=20$)	(4.0)	(17.8)	—	—	(22.0)	(0.42)
Tea	5.5	28.1	216.0	232.4	64.5	8.06
($n=9$)*	(2.2)	(4.7)	(21.3)	(23.3)	(21.5)	(0.48)
Tea/toast	5.6	30.0	158.7	182 4	73.4	7.29
($n=11$)	(4.8)	(6.6)	(52.6)	(53.7)	(52.7)	(1.33)
Significance	ns	ns	$P<0.03$ (tea *v.* tea + toast)	$P<0.02$	$P<0.02$ (if control *v.* tea and tea + toast combined	$P<0.05$ (control *v* tea + toast mainly)

RESULTS

These are shown in table I. For the purpose of statistical analysis the patients were divided into the control group of 20, a group who received tea only (nine) and those who had eaten a breakfast of tea and toast (11). In the control group the average volume aspirated was 33.2 ml (SD 22.0, range 5–95 ml) with a mean pH of 8.24 (SD 0.42, range 7.38–8.99). This compared with an average volume of 64.5 ml (SD 21.5, range 0–93) and pH 8.06 (SD 0.48, range 6.98–8.40) in those who received tea only, and a mean volume of 73.4 ml (SD 52.7, range 16–184) and pH 7.29 (SD 1.35, range 4.54–8.79) in those who had consumed both tea and toast. As the values had a rather skewed distribution, the groups were compared using Mann–Whitney two-sample tests.

The difference of volume aspirated between groups was significant ($P \leqslant 0.02$) if one compared the control group with the tea, and tea-and-toast, group as a whole. There was no significant difference between the tea only and tea-and-toast groups. Although the difference in pH between the tea only and the tea-and-toast groups almost reached statistical significance, when the pH was adjusted for regression on interval, any evidence of a difference between the tea only and the tea-and-toast groups disappeared. However, the difference in pH between control and fed groups achieved statistical significance ($P \leqslant 0.05$). It may be seen from table I that, by chance, the interval between breakfast consisting of tea only and induction was significantly longer than the interval between breakfast consisting of tea and toast and induction ($P \leqslant 0.03$).

The nature of the aspirate was also observed and in only two patients were there recognizable particles of toast. The incidence of nausea and vomiting in the postoperative period in the whole series was low (20%). This compares well with the incidence of nausea and vomiting following operation in elective Caesarean sections under general anaesthesia in this hospital (18.5% for the year 1984).

DISCUSSION

It is recommended that patients undergoing elective surgery under general or local anaesthesia are fasted for 4 h (Gregory, 1984), the aim being to minimize the volume of the gastric contents and decrease the likelihood of their aspiration into the lungs. The latter has been well documented with regard to obstetric patients, Mendelson (1946) having initially reported a series of patients suffering from the acid aspiration syndrome which bears his name, as well as two deaths from asphyxia resulting from complete tracheal obstruction by solid food particles. Acid aspiration continues to feature regularly in the triennial Report of Confidential Enquiries into Maternal Deaths in England and Wales, and in the 1976–1978 report 14 of the 30 deaths attributed directly to anaesthesia were the result of acid aspiration. However, only nine of these patients had definitely been given antacids and no mention of food particles was made in the report.

It has been shown to be safe to offer the non-obstetric patient a "light" breakfast of tea and toast. Does the same apply to the obstetric patient undergoing an elective procedure? Gastric emptying is normal in the obstetric patient at term (Hytten and Chamberlain, 1980) and is only delayed when the patient has either been in prolonged labour or received narcotics (Nimmo, Wilson and Prescott, 1975). The unpremedicated obstetric patient awaiting elective surgery is, therefore, the equal of her non-pregnant counterpart from this viewpoint. However, the volume of gastric contents is increased whilst pH is decreased, probably as a result of increased gastrin concentrations (Attia et al., 1982). In addition, intra-abdominal pressure is increased, thus enhancing the risk of aspiration of gastric contents. Does the ingestion of food enhance that risk by further increasing the volume of gastric contents, decreasing the effect of an antacid regimen by dilution, and the possibility of aspiration of food particles?

The maximum volume of gastric contents in the breakfasted group as a whole was double that of the fasted group: 184 ml compared with 95 ml. Those who drank tea only had volumes (maximum 93 ml) similar to those in the fasted group. A concomitant decrease in the pH of the gastric contents in the breakfast group was noted, the lowest pH recorded in this group being 4.54 compared with 7.38 in the control group. Although this is above the recommended pH of 3.5 (Teabeaut, 1962; Taylor, 1975), 30% of those in the breakfasted group had a pH less than 7.0, whilst none in the control group did. One patient in the tea only group had a pH of 6.98. Finally, food particles were noted in two of the gastric aspirates. Aspiration of food particles into the lungs can lead to an extensive bronchiolitic obstruction of the airway as well as subsequent development of an obliterative bronchiolitis (Moran, 1951; Wynne et al., 1979).

Therefore, we recommend that, despite the fact that no harm came to any of these patients, the normal overnight fast was resumed in this hospital as, unlike Miller, Wishart and Nimmo (1983), we found that in the pregnant patient a light breakfast of tea and toast about 2–3 h before surgery, did influence the volume and pH of the gastric contents.

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INFLATION PRESSURE, GASTRIC INSUFFLATION AND RAPID SEQUENCE INDUCTION

E. G. LAWES, I. CAMPBELL AND D. MERCER

SUMMARY

An investigation was carried out into the relationship between the inflation pressures of normally compliant lungs and the airways pressure necessary to produce the insufflation of gas to the stomach. This relationship was examined during manual ventilation with a mask, using a rapid sequence induction technique. In the absence of cricoid pressure the lungs of all the patients could be ventilated "gently" satisfactorily by hand without gas entering the stomach. In only half of the patients could gas be redirected to the stomach when maximal inflation pressures were generated. It was not possible to cause gas to enter the stomach in any patient with a patent airway when cricoid pressure was applied.

Manual inflation of the lungs should be avoided (before tracheal intubation) when rapid sequence induction is performed. This teaching is applied to all patients at risk from the dangers of a full stomach, particularly in obstetric practice. Unless hypoxia supervenes, manual ventilation is contraindicated on two grounds. First, if cricoid pressure has been inadequately applied (a not uncommon situation (Howells et al., 1983)), silent regurgitation may occur and gastric contents be forced into the lungs. Second, and more importantly, it has been stated that manual inflation of the lungs can lead to gaseous distension of the stomach and further predispose to vomiting or regurgitation, or both (Snow, 1963).

With the use of adequate preoxygenation and a rapidly-acting depolarizing neuromuscular blocking agent, manual ventilation of the lungs before intubation is not usually required. Under certain circumstances, however, the patient's oxygen reserves may be insufficient as, for example, during failed or delayed intubation—particularly when the oxygen reserves are decreased (low FRC) (Nunn, 1977), or when oxygen consumption is increased as during pregnancy (Archer and Marx, 1974), thyrotoxicosis or fever.

Similarly, when suxamethonium is contraindicated, the speed of onset of a non-depolarizing agent may be adequate to allow intubation before the exhaustion of the oxygen reserves.

Recently, the "priming" principle has been described (Gergis et al., 1983; Foldes, 1984; Miller, 1985; Schwarz et al., 1985). A non-depolarizing agent is used as an alternative to suxamethonium when this agent is contraindicated for rapid sequence induction. The principle appears to enable laryngeal intubation to be achieved within a time span more usually associated with the use of suxamethonium. In our view it is still a situation under which the combination of cricoid pressure and manual inflation would be anticipated to occur most frequently.

The purpose of this study was to determine the relationship between the inflation pressures required to ventilate normally compliant lungs, and those pressures required to produce distension of the stomach. Pressures were investigated following the "priming" technique for rapid sequence induction, with and without cricoid pressure, using atracurium as the sole neuromuscular blocking agent.

MATERIALS AND METHODS

Twenty unselected, starved patients drawn from routine operating lists, who had standard indications for tracheal intubation, were studied. No

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patient gave any history of respiratory tract disease. The study was carried out with ethical committee approval.

Before starting the anaesthetic sequence a stethoscope with an extension was taped over the epigastrium in order to auscultate the upper abdomen. (Before commencing the definitive study, it had been determined (in a pilot study) that it was possible—by auscultating over the epigastrium—to detect gas volumes of as little as 5 ml entering the stomach from the oesophagus.) Five to six minutes before the induction of anaesthesia a "priming" dose of atracurium 0.04 mg kg^{-1} was administered. A "sleep" dose of thiopentone 3–4 mg kg^{-1} was then followed by the intubating dose of atracurium to bring the total dose of atracurium to 0.4 mg kg^{-1}.

In order to measure inflation pressures a Lack anaesthetic breathing system and a face mask were connected via a modified angle piece to an aneroid pressure gauge (range −2 to +100 cm H_2O). Following the induction of anaesthesia the face mask was closely applied and gentle inflation of the lungs was achieved using a mixture of nitrous oxide, oxygen and halothane (fresh gas flow 9 litre min^{-1}). The pressure generated in response to a clinically acceptable respiratory excursion was recorded during auscultation over the epigastrium to detect any gas entry to the stomach. The expiratory valve was closed and a careful assessment made to ensure that no leak occurred around the mask. Manual inflation was repeated and the maximum or "peak" inflation pressure recorded, while the stomach was again auscultated. The same procedure was repeated during the application of cricoid pressure.

RESULTS

The mean age of the patients was 47 yr (SD 17; range 16–80). The mean weight was 68 kg (SD 9.2; range 53–83 kg). The mean inflation pressure required to achieve clinically adequate respiratory excursions was 16.5 cm H_2O (SD 8; range 8–35 cm H_2O).

The mean value for "peak" pressures was 31.2 cm H_2O (SD 6; range 20–40 cm H_2O). The "peak" pressure was taken as either the maximum pressure that could be generated by the system, even without air entering the stomach, or the pressure at which gas entered the stomach, whichever occurred sooner. Eleven patients were inflated to the "peak" pressure without evidence of gastric inflation (mean 30 cm H_2O). In the other nine the "peak" pressure recorded represents the pressure at which air was noted to have entered the stomach (mean 33.6 cm H_2O). There was no statistically significant difference between these two pressures. The mean "peak" circuit pressure generated during the application of cricoid pressure was 44.7 cm H_2O (SD 7.2; range 30–60 cm H_2O). On no occasion did air enter the stomach when the airway was patent during the application of cricoid pressure—irrespective of the pressures generated. In two of the oldest patients cricoid pressure not only effectively occluded the oesophagus, preventing the passage of gas into the stomach, but also prevented its passage into the lungs. In one patient cricoid pressure resulted in obstruction of the larynx but allowed gas to enter the stomach. On no occasion did gas enter the stomach during the application of "gentle" inflation pressures (as judged by a clinically acceptable respiratory excursion).

In the absence of cricoid pressure the minimum pressure required to cause gas to enter the stomach, as determined by auscultation, was 20 cm H_2O. When air entered the stomach as a result of deliberately increasing the airway pressure, it could be detected instantly by a stethoscope placed over the epigastrium. Gas did not enter the stomach in any patient with a patent airway when cricoid pressure was applied, despite inflation pressures exceeding 60 cm H_2O on occasion.

DISCUSSION

Using the "priming" principle during the rapid sequence induction technique, we have demonstrated that no gas entered the stomach during normal ("gentle") inflation of the lungs before intubation, even in the absence of cricoid pressure.

There are few reports in the literature to clarify the relationship between inflation pressures and the airway pressure(s) required to divert gas into the stomach. Following tracheal intubation O'Mullane (1954) placed a bolus of fluid in the pharynx, and using "strong" inflation of the bag via a mask, in the absence of cricoid pressure, found that no fluid was lost down the oesophagus. Sellick (1961), in his original article on cricoid pressure, suggested that the correct application of this manoeuvre would prevent the passage of gas down the oesophagus. Ruben, Krudsen and Carngati (1961) investigated this problem in relation to the position of the head, with and without "forceful pressure on the anterior surface of the neck, against the thyroid and cricoid cartilages". Although these investigations seem similar to our own, they differ on a number of important points. First, the measurements were obtained under static conditions following full neuromuscular blockade—not during the induction phase. Second, the second line of defence against fluids travelling up or down the oesophagus, the cricopharyngeus, was breached by "insufflating via wide-bore tubes" placed beyond the cricopharyngeus. These authors reported that gastric inflation rarely occurred when pressures of less than 15–20 cm H_2O were applied, a result very similar to our own. They also reported that, in general, tidal volumes in excess of 1 litre were required to achieve this range of inflation pressures.

More recently, Vyas, Milner and Hopkin (1983) studied face mask resuscitation and gastric distension in neonates, and obtained results similar to our own. They stated that gastric distension in neonates did not occur unless a high mean airway pressure of 30 cm H_2O was exceeded. They concluded that resuscitation using a bag and mask, even in the absence of cricoid pressure, should not lead to gastric distension, provided the inflation pressure never exceeded 20 cm H_2O.

From our own results it appears that the value of "gentle" inflation pressure (that sufficient to produce a clinically acceptable respiratory excursion) has a wide range (8–35 cm H_2O), an observation at variance with the concept of the "educated hand". We found an overlap between the range of inflation pressures required for adequate ventilation and those producing gastric insufflation. However, in any individual patient no gastric insufflation occurred before a clinically acceptable respiratory excursion was produced. In some patients, the two pressures were within 5 cm H_2O of each other, but only in the absence of cricoid pressure.

Cricoid pressure in the elderly may result in laryngeal obstruction. In one patient in this study the application of cricoid pressure caused more of an obstruction to the larynx than to the oesophagus, resulting in diversion of all the gas to the stomach. The inflation pressure at which this occurred was 45 cm H_2O, a value rarely encountered in routine practice. The knowledge that normally applied cricoid pressure can completely obstruct the larynx in elderly patients may be of benefit when massive pharyngeal soiling may occur suddenly and unexpectedly. The apparent ease with which the larynx can be distorted in this age group may indicate that the rapid application of cricoid pressure might permit the pharynx to be evacuated before tracheal soiling occurs.

In this investigation atracurium and the "priming" technique were used deliberately as this would appear to be the circumstance under which the combination of manual inflation and cricoid pressure would, in our view, be required most frequently. Although "priming" would appear to give significantly faster intubating times than standard techniques with non-depolarizing agents, even this modification may be insufficient to allow an appropriate margin of safety against hypoxia. Under these circumstances manual inflation of the lungs would be necessary while cricoid pressure is being applied.

Air entry to the stomach, when it occurred, ceased immediately once the manual inflation was discontinued. All patients were ventilated successfully without producing gastric distension, even without cricoid pressure. Should the fear of gastric distension continue to cause anxiety during manual ventilation, the situation can be effectively monitored and controlled by the use of an epigastric stethoscope and a pressure gauge in the breathing system.

In conclusion, we were unable to substantiate the statement that manual inflation of the airway should be avoided during rapid sequence induction on the grounds that it will lead to gastric distension. The application of cricoid pressure effectively prevents gastric distension *provided the airway remains clear*.

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CONTINUOUS EXTRADURAL ANALGESIA IN LABOUR

Comparison Between "On Demand" and Regular "Top-up" Injections

G. PURDY, J. CURRIE AND H. OWEN

Pain relief during labour is provided frequently by the injection of local anaesthetic to the extradural space. During continuous extradural blockade the intermittent injection of local anaesthetic in response to the return of pain ("top-up" on demand) has been described as the method of choice, in the belief that the total dose of local anaesthetic is minimized (Bromage, 1978). By definition, extradural "top-up" injections given "on demand" condemn the patient to painful intervals, and when lignocaine is used to provide extradural analgesia, interanalgesic intervals encourage the development of tachyphylaxis (Bromage, Pettigrew and Crowell, 1969).

The regular administration of incremental doses of local anaesthetic, given at suitably timed intervals before pain returns (truly continuous extradural blockade), may avoid tachyphylaxis and result in the administration of a lower total dose of local anaesthetic. This technique could have advantages over more conventional therapy. More patients may be satisfied if the analgesia they request is continuous and, since the degree of concomitant sympathetic blockade will fluctuate little, there may be less cardiovascular instability following top-ups. On the other hand, the administration of extradural top-ups at fixed time intervals may result in the patient receiving more agent than required and so increase the degree of motor blockade, extend the sensory blockade, and increase the requirement for operative delivery.

This study was undertaken to compare the techniques of regular and on demand extradural injections of bupivacaine for pain relief during uncomplicated full-term labour.

SUMMARY

In a prospective comparative study 240 patients received extradural bupivacaine, either by regular timed injections or "on demand", for pain relief during the first stage of labour. Three concentrations of bupivacaine were used (0.5%, 0.375% and 0.25%). Quality and continuity of analgesia, motor blockade, spread of sensory blockade, cardiovascular changes, fetal outcome and maternal sequelae were recorded. Overall, the analgesia provided by regular top-up injections was superior to the on demand technique, especially when 0.375% bupivacaine was used. This improved analgesia was achieved without causing an increased incidence of operative deliveries or deleterious sequelae, with respect to the mother or the neonate.

PATIENTS AND METHODS

In accordance with local hospital practice, the study was approved by inter-departmental peer review. Two hundred and forty consecutive patients who requested extradural analgesia for pain relief during the first stage of labour gave their informed consent to enter the study. Patients were randomly allocated to six groups of similar size to receive 0.5%, 0.375% or 0.25% bupivacaine, administered either by regular timed injections, or on demand when the contractions became painful.

The technique of extradural blockade was similar in all patients. An i.v. infusion was commenced and 300–500 ml of lactated Ringer's solution was administered. Using an 18-gauge Tuohy needle, 3–5 cm of extradural catheter was introduced to the extradural space at either the L2–3 or the L3–4 space. An initial "test dose" of 2 ml of bupivacaine solution, of the designated concentration, was followed after 3 min by a volume sufficient to achieve a total dose of agent

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equivalent to 0.5 mg kg^{-1}. Subsequently, each top-up injection consisted of the same dose administered as 0.25%, 0.375% or 0.5% bupivacaine. One hundred and twenty patients were allocated to receive this dose at 90-min intervals throughout the first stage of labour, unless an earlier top-up was requested. The same number were to receive the same dose on demand when blockade had diminished, and the contractions became painful.

The upper and lower limits of sensory blockade were measured by pinprick 30 min after each top-up. Patients, in the regular groups in whom the upper level of sensory blockade exceeded the level of T4, and who were pain free when a top-up was due, did not receive another until the next appointed time—provided the block had receded. Analgesia was assessed on a four-point scale (0 = no pain; 1 = discomfort; 2 = moderate abdominal pain; 3 = severe abdominal pain) immediately before, and 30 min after, each extradural top-up.

Motor blockade was measured on a five-point scale (0 = total paralysis; 1 = can move leg in a horizontal plane only; 2 = can raise leg against gravity but not against resistance; 3 = slightly reduced power but can still raise leg against gravity and resistance; 4 = normal power) 30 min after each top-up. If a patient in the regular top-up group complained of unacceptable motor blockade when a top-up was due then, in the absence of pain, the top-up was withheld until the next appointed time. Heart rate and arterial pressure were measured before, and at 5-min intervals for 15 min after, each top-up.

Patients who received only one dose, or in whom the initial degree of blockade was unsatisfactory were withdrawn from the study. The mode of delivery, Apgar score and any paediatric or obstetric complications were recorded. On the day following delivery, the patients were interviewed by an investigator who was unaware of which injection technique had been used to provide pain relief, and the patient's impressions about the quality and continuity of analgesia, the inconvenience of motor blockade and overall satisfaction with analgesia were obtained.

Statistical analysis

Unpaired Student's *t* test was used in the comparison of height, weight, age, arterial pressure, changes in heart rate, number of segments blocked and degree of motor blockade. The Mann–Whitney *U* test was used in the analysis of parity and Apgar scores. Data for the mode of delivery and analgesia were analysed using the Chi squared test. A *P* value of less than 0.05 was accepted as being statistically significant.

RESULTS

The characteristics of the patients are presented in table I. There were no significant differences between the six groups. Patients who received regular top-ups appeared to have better continuity of analgesia as assessed on a four-point scale. Eighty-four percent of patients given 0.375% bupivacaine, 76% of the patients given 0.25% bupivacaine and 43% of patients given 0.5% bupivacaine regularly were completely pain free throughout the period of observation (table II). All patients receiving their incremental doses on demand experienced some pain during the period of observation. There were no differences in the subjective quality of analgesia between the regular and on demand groups who received 0.5% and 0.25% bupivacaine (table III). However, with 0.375% bupivacaine the regular group had a significantly better quality of analgesia than the corresponding on demand group ($P < 0.01$).

Changes in arterial pressure and heart rate after top-ups were similar in all groups. Using the

TABLE I. *Patient data (mean ± 1 SD). Bup. = bupivacaine; reg. = regular top-ups; dem. = on demand top-ups*

Group	Agent	*n*	Age (yr)	Height (cm)	Weight (kg)
R1	0.5% Bup. reg.	41	22.8±4.1	159.4±7.1	70.8±10.5
D1	0.5% Bup. dem.	39	24.6±4.6	159.2±7.6	73.7±13.9
R2	0.375% Bup. reg.	38	23.7±4.7	157.9±7.7	68.9± 9.4
D2	0.375% Bup. dem.	42	23.7±4.0	159.1±7.7	67.4±14.3
R3	0.25% Bup. reg.	41	24.5±5.1	158.2±6.9	69.7±10.8
D3	0.25% Bup. dem.	39	24.5±5.0	158.6±6.6	71.4±12.9

TABLE II. *Numbers of patients who experienced pain during extradural analgesia. The maximum severity only is recorded for each patient*

Group	Severe	Moderate	Mild	None
R1	5 (12%)	5 (12%)	13 (32%)	18 (44%)
D1	12 (31%)	22 (56%)	5 (13%)	0
R2	0	2 (5%)	4 (10%)	32 (84%)
D2	13 (31%)	23 (55%)	6 (14%)	0
R3	0	5 (12%)	5 (12%)	31 (76%)
D3	13 (33%)	20 (51%)	6 (15%)	0

TABLE III. *Quality of analgesia*

Group	Very good	Good	Satisfactory	Poor
R1	32 (78%)	5 (12%)	2 (5%)	2 (5%)
D1	24 (62%)	13 (33%)	1 (2%)	1 (2%)
R2	33 (87%)	4 (11%)	1 (2%)	0
D2	18 (43%)	16 (38%)	6 (14%)	2 (5%)
R3	30 (73%)	8 (20%)	3 (7%)	0
D3	25 (64%)	9 (23%)	5 (13%)	0

definition (Abboud et al., 1984) of maternal hypotension as a decrease in systolic arterial pressure of more than 30 mm Hg or to less than 100 mm Hg, there were eight cases of hypotension in this study: three patients were in the regular group, and five in the on demand group. All responded to an increase in the rate of administration of i.v. fluids.

The number of spinal segments blocked after each of the first three top-up injections were compared (the numbers of patients who received more than three top-up injections were inadequate for statistical analysis). There was no difference in the extent of sensory blockade between the six groups, but there were six patients, receiving regular top-ups, who had top-up injections withheld because the block had reached T4. Four of these patients had received 0.5% bupivacaine and two had received 0.25% bupivacaine. There were significant differences in the lower limit of block between some regular and on demand groups (table IV). Patients who received 0.25% bupivacaine regularly had a consistently greater degree of sacral blockade than the corresponding on demand group with each top-up. No consistent difference was found with the other concentrations.

There were no differences in the degree of motor blockade between any group. Four patients requested that a top-up be withheld because they had excessive leg weakness; all were receiving regular injections of 0.25% bupivacaine. Six patients complained of excessive weakness following parturition: all had received 0.5% bupivacaine, three on demand and three regularly. Six patients in the regular groups, four of whom received 0.5% bupivacaine and two of whom received 0.25% bupivacaine, required a top-up injection within 90 min of the previous dose.

Fetal outcome measured by Apgar scores at 1 and 5 min was unaffected by the technique used to administer the incremental doses. Only three neonates had very low Apgar scores, but all responded promptly to resuscitation. In all three instances the mother had received extradural analgesia on demand. The mode of delivery was unaffected by the technique used (table V). However, the concentration of local anaesthetic used was an important factor. There was a greater incidence of operative deliveries in those patients who received 0.25% bupivacaine compared with patients who received 0.375% bupivacaine.

The mean dose of bupivacaine administered was similar in the groups receiving 0.5% and 0.375% bupivacaine, but the group receiving regular injections of 0.25% bupivacaine were given significantly more than the corresponding on demand group. The total dose administered was governed by the duration of labour, and the time interval between successive doses is a better guide to the duration of action of the local anaesthetic (table VI). The number of patients

TABLE IV. *Number of segments blocked below T10 (mean ± 1SD).* *$P < 0.05$; ** $P < 0.01$

Group	Dose 1	Dose 2	Dose 3
R1	4.17 ± 1.38 ($n = 41$)	4.85 ± 1.30 ($n = 41$)	5.16 ± 0.94 ($n = 25$)
D1	4.36 ± 1.18 ($n = 30$)	5.08 ± 1.20 ($n = 39$)	5.45 ± 1.18 ($n = 22$)
R2	3.57 ± 0.97 ($n = 38$)	4.95 ± 1.11 ($n = 38$)**	4.70 ± 1.17 ($n = 19$)
D2	3.97 ± 0.67 ($n = 42$)	4.26 ± 0.91 ($n = 42$)	4.78 ± 1.00 ($n = 18$)
R3	4.07 ± 1.08 ($n = 41$)	4.78 ± 0.96 ($n = 41$)*	5.00 ± 1.27 ($n = 21$)**
D3	3.69 ± 1.00 ($n = 39$)	4.33 ± 0.70 ($n = 39$)	3.75 ± 1.06 ($n = 19$)

TABLE V. *Mode of delivery. SVD = Spontaneous vaginal delivery; LCFD = low cavity forceps delivery; MCFD = mid cavity forceps delivery; CS = Caesarean section*

Group	SVD	LCFD	MCFD	CS
R1	21	5	10	5
D1	21	3	12	3
R2	22	0	11	5
D2	22	3	7	10
R3	17	2	19	3
D3	16	3	14	6

receiving three or four top-up injections was small and we have not drawn conclusions from these results. The lengthening interval in the regular 0.5% and 0.25% groups was the result of top-up injections being withheld.

The majority of patients in the study were pleased with the analgesia they received. Ten of the 240 said they would not request extradural analgesia again during a subsequent labour; five received extradural analgesia on demand. There were no serious sequelae recorded during the course of this study.

DISCUSSION

The major finding of this study was that regular extradural top-up injections with bupivacaine produced analgesia superior to that from conventional on demand therapy. This was obtained without apparently increasing the incidence of deleterious sequelae, in terms of operative deliveries, neonatal wellbeing and maternal health.

In order to provide truly continuous extradural blockade, most studies have recommended the continuous infusions of local anaesthetic agents whether during labour (Scarborough, 1972; Matouskova and Hanson, 1979; Taylor, 1983) or for the relief of postoperative pain (Ross, Clarke and Armitage, 1980; Scott, Schweitzer and Thorn, 1982). There are several advantages of this method: fewer painful intervals, less motor blockade, lower risk of infection with a closed system, greater cardiovascular stability, and a lower likelihood of a serious complication following accidental subarachnoid or i.v. injection. Despite some encouraging results, this technique has not gained widespread acceptance, possibly because occasional top-up injections are still required and a higher total dose of local anaesthetic is administered. Thus the discontinuous technique of intermittent extradural injection on demand still predominates in obstetric practice (Bromage, 1978).

We have not found any major studies on regular extradural top-up injections in labour, although favourable results have been obtained with regular top-up injections for the relief of postoperative pain. Automatic devices to administer regularly-timed extradural injections have been described (Cox and Spoerel, 1964; Scott, Schweitzer and Thorn, 1982), but there is only one study of their use during labour (Spoerel, Thomas and Gerula, 1970).

TABLE VI. *Time intervals (min) between successive extradural top-up injections (mean ± 1 SD; range; number of patients at each interval for each group)*

Group	First interval	Second interval	Third interval	Fourth interval
R1	89.2 ± 10.6 $n = 41$ 30–180	92.6 ± 18.5 $n = 25$ 75–180	96.4 ± 24.1 $n = 14$ 90–180	102.9 ± 34.0 $n = 7$ 90–180
D1	105.7 ± 41.59 $n = 39$ 30–265	114.77 ± 32.2 $n = 22$ 30–170	101.5 ± 40.1 $n = 10$ 30–185	98.3 ± 42.5 $n = 3$ 50–130
R2	90 ± 0 $n = 38$	90 ± 0 $n = 19$	90 ± 0 $n = 12$	90 ± 0 $n = 6$
D2	98.1 ± 37.4 $n = 42$ 25–180	118.1 ± 37.4 $n = 18$ 80–210	115.7 ± 38.9 $n = 14$ 60–190	108.0 ± 25.1 $n = 5$ 75–140
R3	87.7 ± 8.5 $n = 41$ 50–90	85.2 ± 12.9 $n = 21$ 40–90	106.9 ± 33.5 $n = 8$ 90–180	130 ± 45.9 $n = 3$ 90–180
D3	124.25 ± 42.4 $n = 39$ 60–225	134.7 ± 42.5 $n = 19$ 70–230	86.4 ± 22.1 $n = 7$ 50–120	95.0 ± 32.1 $n = 3$ 60–125

The dose of bupivacaine administered in the present study was based on that used routinely in our obstetric unit, and the time interval selected for patients who received regular, timed extradural top-up injections was based on the authors' previous experience of extradural anaesthesia (Owen et al., 1986). Plain solutions of bupivacaine were used because many authors consider this to be the agent of choice (Moir, 1980; Henderson and Nimmo, 1983). Bupivacaine 0.125% was not used as the results in previous studies were not encouraging (Stainthorp et al., 1978; Li, Rees and Rosen, 1985).

Among the patients who received regular top-ups, there was a higher incidence of painful intervals in patients receiving 0.5% bupivacaine than in the other two groups. This was predominantly the result of a higher incidence of rectal discomfort in the former group. It is possible that the smaller volume used in this group was associated with less caudal spread, less sacral blockade and, hence, more rectal discomfort.

We did not find better cardiovascular stability in the regular groups when compared with the on demand groups. The overall incidence of maternal hypotension was 3.3% which concurs with the findings of other authors (Crawford, 1975; Moir, 1980). Provided patients receive an adequate i.v. fluid preload and aorto-caval compression is avoided, maternal hypotension is uncommon.

Overall, the average rate of administration of extradural bupivacaine for the trial groups was 0.33 mg kg^{-1} h^{-1}, which was less than the recommended upper dose limit of 2 mg kg^{-1} over a 4-h period (*British National Formulary*, 1985). Patients who received 0.5% and 0.375% bupivacaine regularly, however, did not receive any more bupivacaine than the corresponding on demand groups. Tachyphylaxis may occur during continuous extradural analgesia. One component of this phenomenon may be the interanalgesic intervals between top-ups (Bromage, Pettigrew and Crowell, 1969). Top-up injections are usually administered on demand; however, when the preceding dose has been allowed to wear off a decay in response can be expected. We found no evidence of tachyphylaxis with bupivacaine but, although we have studied a large number of patients, few received more than three incremental injections. In most work on tachyphylaxis lignocaine has been used, and tachyphylaxis has occurred after the administration of several doses.

We have found 0.375% bupivacaine to be the most suitable concentration for extradural analgesia in labour provided by regular top-up injections. It provided an adequate level of analgesia and appropriate sensory blockade, without excessive motor blockade. Our results suggest this concentration of bupivacaine provides a lower incidence of painful intervals than 0.5% bupivacaine, when given regularly. In addition, this concentration is associated with a lower incidence of operative deliveries than is 0.25% bupivacaine, however administered. Regular extradural top-up injections to prevent pain in labour may be an improvement on the traditional technique of pain therapy and the technique deserves further investigation.

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EXTRADURAL INFUSION OF 0.125% BUPIVACAINE AT 10 ML H^{-1} TO WOMEN DURING LABOUR

D. G. BOGOD, M. ROSEN AND G. A. D. REES

Continuous extradural analgesia is now used widely to relieve pain in labour. However, to maintain pain relief throughout labour, one or more incremental doses of local anaesthetic agent are usually required. Each "top-up" may be preceded by a period of increasing pain for the patient, and involves heavy demands on midwifery and anaesthetic staff. In addition, it may cause significant alterations in the maternal cardiovascular system. Any method that could prolong the interval between top-ups safely is desirable, and continuous infusions of local anaesthetic agents through the extradural catheter have been tested (Glover, 1977; Evans and Carrie, 1979; Matouskova, Hanson and Elmen, 1979; Davies and Fettes, 1981; Abboud et al., 1983; Kenepp, Cheek and Gutsche, 1983; Taylor, 1983; Li, Rees and Rosen, 1985).

The risk of subdural migration of the catheter tip during the course of labour would suggest that the lowest concentration and dose of local anaesthetic agent compatible with significant prolongation of blockade should be used when an infusion is used. Li, Rees and Rosen (1985) reported an optimum rate of 10 ml h^{-1} of 0.125% bupivacaine as satisfying these criteria. The present study was designed to assess this regimen further, with particular emphasis on the overall safety of the technique, and on any adverse effects in the mother or the baby.

PATIENTS AND METHODS

The study was approved by the local ethics advisory committee. The techniques and measurements were in regular use in our units, so no further consent was necessary except that usually obtained for the placement of an extradural catheter.

The study included primigravid mothers admitted to two maternity units in Cardiff, because primigravidae are expected to have longer and more complicated labours. Only mothers in established labour (confirmed by cervical dilatation) who requested or accepted extradural analgesia for pain relief were included.

I.v. access was established in the patient's non-dominant hand and a rapid infusion of Hartmann's solution was commenced. The extradural block was performed by the duty anaes-

SUMMARY

One hundred primigravidae were allocated randomly to receive either an extradural infusion of 0.125% bupivacaine (Marcain) 10 ml (12.5 mg) per hour during labour, or no infusion. Both groups had intermittent "top-ups" of 0.5% bupivacaine when indicated. The mean interval between top-ups was significantly longer in the infusion group (218 min v. *152 min). Seventy-six percent of the mothers in the infusion group required no or only one top-up. Although the infusion patients received a higher mean dose of bupivacaine (178 mg* v. *130 mg), there was no difference between the groups with respect to mode of delivery, need for urinary catheterization, adverse cardiovascular effects on mother or fetus, or the time taken after delivery to recover sensation and motor power. The only real disadvantage was that the infusion group had an increased incidence of lower limb weakness (64%* v. *44%). The neonates had similar Apgar scores, times to sustained respiration and requirements for resuscitation. The technique, therefore, should be safe if coupled with testing of sensory level, as no block extended higher than T6.*

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TABLE I. *Patient data (mean (SD))*

	Age (yr)	Weight (kg)	Height (cm)	Birth wt (g)	Cervical dilatation at time of extradural (cm)
Infusion	23.8 (4.2)	69.1 (12.9)	159.9 (4.9)	3318 (539)	4.1 (1.5)
Control	24.1 (4.7)	66.9 (12.7)	158.4 (5.5)	3343 (475)	4.2 (1.6)

thetist with the mother in either the left lateral or sitting position. An interspace between L1 and L5 was used and 0.5% bupivacaine (Marcain) 6–10 ml administered through a bacterial filter. No special instructions were given regarding positioning the patient, except for those used routinely to avoid the supine hypotensive syndrome. Following our usual practice, the block was assessed for 20 min and further increments of bupivacaine were administered, if necessary.

Patients were allocated randomly to receive either an infusion of 0.125% bupivacaine in 0.9% sodium chloride solution (prepared by the pharmacy) at 10 ml h^{-1} by an IMED 928 volumetric pump, or no infusion. Patients from both groups were treated with top-up doses of 0.5% bupivacaine (0.25% in a few cases) by the anaesthetist when pain returned. The infusion and top-ups continued throughout the second stage of labour. Following the start of the infusion and after each top-up, arterial pressure and fetal heart rate were recorded every 5 min for 25 min and thereafter every 30 min.

The duration of each stage of labour and the mode of delivery were recorded. The time from the siting of the extradural catheter to delivery, the number of top-ups, the interval between top-ups and the total dose of bupivacaine administered were calculated. The maximum decrease in maternal arterial pressure and the slowest fetal heart rate were noted, along with the incidence of excessively high blockade, the number of unblocked segments and the need for catheterization during and after labour. The maximum degree of motor blockade was assessed on a four-point scale according to the ability of the mother to move her legs against resistance.

Each mother was questioned on the day after delivery about the time taken for sensation and power to return to her legs. She was asked how helpful the extradural block had been, and whether she would have it again. Neonates were assessed using the Apgar score at 1 and 5 min as well as the time to sustained respiration and any need for resuscitative measures.

Parametric data were analysed by Student's *t* test, and the Chi-squared test with the Yates' correction, where applicable, was used on non-parametric data.

RESULTS

One hundred primigravidae were studied, 50 in each group. The groups did not differ with respect to age, height, weight, birth weight and cervical dilatation at the time the extradural catheter was placed (table I).

The progress and outcome of labour are shown in table II. Stage I was significantly longer in the control group (mean 11.1 *v.* 9.5 h ($P < 0.05$)) although there was no significant difference in the time from siting the extradural to delivery (mean 7.0 h. *v.* 6.4 h). Stage II was longer in the infusion group (mean 106 min *v.* 86 min), but the difference was not significant ($0.1 > P > 0.05$). There was no difference between groups in the mode of delivery: 10 patients (20%) in the infusion group had emergency Caesarean sections, compared with nine patients (18%) in the control group. The incidence of forceps/ventouse-assisted deliveries was 52% in the infusion group and 46% in the control group (ns).

If, after a top-up, there was residual pain requiring further small doses to achieve good blockade, these increments have been treated as part of the original top-up. Where good blockade existed already and a further dose of local anaesthetic was given immediately before an instrumental delivery, this last dose has been disregarded when calculating the number of top-ups. In the infusion group (table III) 38 patients (76%) needed no or only one top-up compared with 29 patients (58%) in the control group ($0.05 < P < 0.1$). The mean interval between top-ups was calculated by dividing the

TABLE II. *Progress (mean (SD)) and outcome (No. (%)) of labour. *Significant difference* (P < *0.05*)

	Stage 1 (h)	Stage 2 (min)	Time extradural to delivery (h)	Method of delivery (%) Spont. vertex	Forceps/ ventouse	Emergency C/S
Infusion	9.5*	106.1	7.0	15	26	9
	(4.3)	(58.6)	(2.9)	(30)	(52)	(18)
Control	11.1*	86.5	6.4	17	23	10
	(4.3)	(57.2)	(3.2)	(34)	(46)	(20)

TABLE III. *Extradural doses. Significant differences:* ***P < *0.001;* ****P < *0.005*

	Interval between top-ups (h) (mean (SD))	Total dose of bupivacaine (mg) (mean (SD))	Top-ups (No. (%)) 0	1	2	> 2
Infusion	3.64***	177.9****	16	22	4	8
	(1.5)	(83.4)	(32)	(44)	(8)	(16)
Control	2.54***	129.8****	10	19	8	13
	(0.9)	(69.3)	(20)	(38)	(16)	(26)

TABLE IV. *Adverse effects and recovery from extradural (top half: mean (SD); lower half: No. (%)). *Significant difference* (P < *0.05*). *†Data not recorded for all patients*

	Maximum decrease in systolic AP (mm Hg)	Slowest fetal heart rate (beat min^{-1})	Time to recovery of sensation (h)	Time to recovery of power (h)
Infusion	15.9	121.6	2.8	2.6
	(12.3)	(12.4)	(2.3)	(2.5)
Control	17.3	117.9	2.5	2.6
	(16.6)	(16.5)	(2.5)	(2.6)
	Significant motor block	**Persistent unblocked dermatomes**	**Catheterized during labour**	**Catheterized after labour**
Infusion	32*	13	35†	3
	(64)	(26)	(76)	(6)
Control	22*	16	40†	2
	(44)	(32)	(88)	(4)

extradural to delivery time by the number of top-ups (including the first dose) for each mother. In the infusion group the interval was 218 min compared with 152 min in the control group ($P < 0.001$). Patients in the infusion group received a mean total dose of 178 mg of bupivacaine compared with 130 mg in the control group ($P < 0.005$). No patient in either group showed overt or potential evidence of toxicity related to overdose of local anaesthetic agent.

The mean maximum decrease in systolic arterial pressure from pre-extradural values (table IV) was similar in both groups (16 mm Hg *v.* 17 mm Hg) as was the mean slowest fetal heart rate (122 *v.* 118 beat min^{-1}). Thirty-two patients (64 %) in the infusion group had significant motor blockade of the legs (unable to move against resistance) compared with 22 patients (44 %) in the control group ($P < 0.05$). Thirteen patients (26 %) in the infusion groups and 16 (32 %) in the control group had some problem with residual pain from unblocked segments (ns). No patient had a block higher than T6 on either side. The times until sensation and motor power returned were similar for the two groups (2.8 and 2.6 h *v.* 2.5 and 2.6 h). Thirty-five mothers (76 %) in the

TABLE V. *Neonatal data (No. (%)).*

		Apgar scores			Time to sustained respiration	
		0–3	4–7	8–10	< 1 min	> 1 min
Infusion	1 min	2 (4)	6 (13)	39 (83)	35	12
	5 min	1 (2)	0 (0)	46 (98)	(74)	(26)
Control	1 min	1 (2)	9 (18)	40 (80)	42	8
	5 min	0 (0)	1 (2)	49 (98)	(84)	(16)

	Resuscitation			
	None	Suction only	Suction + oxygen	Suction + oxygen + assisted ventilation
Infusion	8	25	8	6
	(17)	(53)	(17)	(13)
Control	6	27	14	3
	(12)	(54)	(28	(6)

TABLE VI. *Acceptability of extradural (No. (%))*

	Patient assessment				
	Fully satisfied	Considerable help	Some help	No help	Deprived of birth sensation
Infusion	40	8	1	0	1
	(80)	(16)	(2)	(0)	(2)
Control	43	4	3	0	0
	(86)	(8)	(6)	(0)	(0)

	Repeat extradural for next labour?			
	Definitely yes	Definitely no	Yes if necessary	Don't know
Infusion	28	1	20	1
	(56)	(2)	(40)	(2)
Control	30	1	15	4
	(60)	(2)	(30)	(8)

infusion group and 40 (80%) in the control group required urinary catheterization at some time during labour, and three mothers (6%) in the infusion group (two (4%) in the control group) were catheterized after delivery (ns).

Data concerning the neonates are shown in table V. Three mothers from the infusion group are not included: two had twins and there were no twins in the control group, and the third had undergone a laparotomy for peritonitis 24 h before delivery by emergency Caesarean section. Her baby had a 5-min Apgar score of zero, attributable to the mother's poor condition and it was considered that this poor outcome was not related to the use of the extradural technique.

Apgar scores at 1 and 5 min were divided into groups of low (0–3), moderate (4–7) and high (8–10). Eight babies (17%) in the infusion and 10 (20%) in the control group had scores less than 8 at 1 min. All but one in each group registered a high score at 5 min. There were no significant differences between the groups. Thirty-five neonates in the infusion group (74%) compared with 42 (84%) in the control group achieved sustained respiration within 1 min (ns). Forty-one neonates (82%) in the infusion group required no resuscitation, apart from suction and oxygen by mask, as compared with 47 (94%) in the control group (ns). Nine neonates needed assisted ventilation using a mask or tracheal tube—six in the infusion group and three in the control group. Two of these babies, both in the infusion group, were delivered by emergency Caesarean section under general anaesthesia and all of the others had been delivered by forceps. None of the neonates (apart from the patient mentioned above) needed transfer to a special care unit.

Forty mothers (80%) in the infusion group were fully satisfied with their extradural analgesia as compared with 43 mothers (86%) in the control group (ns) (table VI). Twenty-eight mothers (56%) in the infusion group and 30 (60%) in the control group would certainly have another extradural for their next labour. Only one patient in each group said that she would definitely not repeat the experience.

DISCUSSION

Several instances of migration of extradural catheter tips through the dura have been reported (Boys and Norman, 1975; Philip and Brown, 1976; Robson and Brodsky, 1977; Kriz and Jouppila, 1980; Park, 1984), and this must be the major concern of anyone using a continuous extradural technique. Li, Rees and Rosen (1985), using data from studies of intradural bupivacaine, suggested that an infusion of bupivacaine 12.5 mg h^{-1}, if given inadvertently subdurally, would need to continue for 2 h before extending higher than T9–T10, so that regular testing of the level of sensory blockade would give adequate warning of transdural migration. Other studies using continuous infusions of bupivacaine have used doses ranging from 12.5 to 25 mg h^{-1} (Glover, 1977; Evans and Carrie, 1979; Matouskova, Hanson and Elmen, 1979; Davies and Fettes, 1981; Abboud et al., 1983; Kenepp, Cheek and Gutsche, 1983; Taylor, 1983; Li, Rees and Rosen, 1985). Should bupivacaine 25 mg h^{-1} be accidentally administered subdurally, this might extend as high as T4 within 1 h, with potential sequelae of marked hypotension and respiratory embarrassment. Li, Rees and Rosen (1985) showed little clinical advantage with doses greater than 0.125% bupivacaine 12.5 mg h^{-1} and concluded that this regimen was the best compromise between significant prolongation of the block and patient safety.

Kenepp, Cheek and Gutsche (1983) found that, for a given hourly dose, lower concentrations of extradural bupivacaine were more effective than higher concentrations, presumably as a result of the increased volumes administered. Although these findings were not confirmed by our previous study (Li, Rees and Rosen, 1985), it would seem advisable to use the lowest effective concentration in order to minimize the effects of an accidental change in infusion rate.

In this study, the mean interval between top-ups in the infusion group was 218 min, an increase of 43% over the control group, and 76% of the patients receiving the infusion required no or only one top-up. These results agree with the findings of our previous study and that of Matouskova, Hanson and Elmen (1979) who used 0.25% bupivacaine 5 ml h^{-1}, that this technique is effective in reducing the workload associated with intermittent top-ups. These beneficial effects were associated with a higher mean total dose of bupivacaine (178 mg *v.* 130 mg). This also compares closely to the results of our previous trial.

One important aim of the present study was to determine whether this increased dose had any adverse effects upon mother or baby. Table II shows that the infusion did not prolong labour significantly and had no appreciable effect upon the mode of delivery. The incidence of forceps/ventouse extractions in the infusion group (52%) compared favourably to the results in other studies in which higher doses were used. Evans and Carrie (1979), using bupivacaine 25 mg h^{-1}, had a forceps rate of 59% in their primigravid patients. In Taylor's study (1983) patients had infusion rates of bupivacaine varying from 15 to 22.5 mg h^{-1} and 68% of patients (primigravid and multigravid combined) required forceps delivery.

Patients receiving an infusion had a higher incidence of motor blockade than the control group (64% *v.* 44%). However, in all other respects, including cardiovascular stability, need for catheterization and time to recovery, there were no differences between the groups. Our previous study did not appear to show any major differences in lower limb weakness between the two equivalent groups, but the results are not strictly comparable as a different scoring system (Bromage, 1978) was used in the earlier trial.

The high degree of patient satisfaction was unaltered by the use of this infusion regimen. This is perhaps not surprising as there was little delay when a top-up was requested—any period without pain relief was relatively short. However, if the anaesthetist has other demands upon his time—apart from the obstetric unit—there may be a considerable delay before he is free to administer a top-up. In these circumstances, patients requiring frequent top-ups would be helped considerably by the use of an extradural infusion, and this may produce a higher degree of satisfaction. The use of an infusion technique does not diminish in any way the responsibility of the anaesthetist to the mother. A regular assessment, either hourly or at least 2-hourly, of sensory level should be mandatory when a limited (12.5-mg h^{-1}) infusion is being used.

The baby was unaffected by the dose of bupivacaine in the infusion group (table V). These clinical findings correlate with the results of our previous study in which the umbilical vein bupivacaine concentration in the equivalent infusion group was no higher than that in the control group (0.159 *v.* 0.164 μg ml^{-1}), despite a considerably higher maternal venous concentration. In other reports, the umbilical vein concentration was consistently less than 0.25 μg ml^{-1} of bupivacaine, even when the maternal venous value was as high as 0.96 μg ml^{-1} (Glover, 1977; Evans and Carrie, 1979). These results are well below an umbilical vein concentration of 1.6 μg ml^{-1}, the value at which Reynolds and Taylor (1971) predicted toxicity may occur.

This study confirms that an infusion of 0.125% bupivacaine 10 ml h^{-1} is effective in prolonging the interval between extradural top-ups without causing any deleterious effects upon the neonate. The only effect on the mother was a greater degree of lower limb weakness. The increased interval between top-ups should result in fewer periods of pain for the mother, particularly in units where an anaesthetist or midwife is not immediately available to administer a further dose of local anaesthetic. In these circumstances, improved patient satisfaction may be anticipated. As with all extradural techniques in obstetric practice, this method should only be used when rapid anaesthetic attendance can be guaranteed at all times, in case of emergency.

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EXTRADURAL ANALGESIA DURING LABOUR USING ALFENTANIL

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SUMMARY

Sixteen primiparous patients requesting pain relief during labour received a continuous infusion of alfentanil 30 μg kg^{-1} h^{-1} via an extradural catheter. Supplementary (extradural) bolus doses (30 μg kg^{-1}) were administered when deemed necessary. Excellent pain relief was rapidly obtained early in labour in all patients. However, analgesia was inadequate in the latter part of stage I and during the second stage in five of the 16 patients—notwithstanding several additional doses of alfentanil, and bupivacaine had to be administered. No serious maternal side-effects, except nausea, were encountered. Although all neonatal Apgar scores were between 7 and 10, the Amiel-Tison test clearly indicated the existence of neonatal hypotonia. The continuous extradural administration of alfentanil proved to be unsatisfactory for pain relief in labour.

Selective spinal analgesia (Cousins and Mather, 1984) with extradural opioids during labour has several advantages over extradural blockade using local anaesthetic drugs. It does not cause sympathetic blockade or motor paralysis of the lower limbs and should not, theoretically, lead to a higher incidence of instrumental delivery. However, different studies using extradural opioid analgesia during labour show considerable differences in the efficacy of the technique and the usefulness of the various drugs used (Crawford, 1980; Magora, Olshwang and Eimerl, 1980; Perriss, 1980; Carrie, O'Sullivan and Seegobin, 1981; Justins, Francis and Houlton, 1982; Justins, Knott and Luthman, 1983). Furthermore, a major concern exists in regard to the potential for causing ventilatory depression in the newborn.

In this study, alfentanil was chosen because of two pharmacokinetic characteristics: its high plasma protein binding (88.7% in the range 1–100 ng ml^{-1}) and its short elimination half-life (Bower and Hull, 1982). Both decrease the risk of neonatal ventilatory depression when compared with the longer acting opioids.

PATIENTS AND METHODS

Patients

Sixteen primiparous patients with an uncomplicated singleton pregnancy, and with the fetus presenting by the vertex were included in the study on requesting pain relief. All patients gave informed consent. They did not, at any time, receive a systemically administered narcotic drug. Sixteen newborn infants from primiparae who did not have an extradural (or any other form of analgesia) and with approximately the same duration of the first stage served as controls to assess any possible effect of alfentanil on the newborn.

Clinical management

Before inserting the extradural catheter (at the L3–4 space) a vaginal examination was carried out to obtain a reference Bishop score (Bishop, 1964). Intrauterine pressure was monitored subsequently in 10 of the 16 patients (fetal monitoring intrauterine pressure kit, Hewlett–Packard 14099C, connected to a quartz transducer, Hewlett–Packard model 1290A). Uterine activity was expressed in Montevideo Units (the sum of the amplitudes (in mm Hg) of the contractions occurring during a 10-min period (Caldeiro-Barcia and Poseiro, 1960)).

A loading dose of alfentanil 30 μg kg^{-1} diluted

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in saline to a total volume of 10 ml was injected to the extradural space when the parturient first asked for pain relief. This injection was immediately followed by a continuous infusion of 30 μg kg^{-1} h^{-1}. Top-up doses (30 μg kg^{-1}) were given when deemed necessary and 0.2% bupivacaine 10 ml was administered when the analgesia with alfentanil alone became inadequate. The infusion of alfentanil to the extradural space was stopped at the beginning of the second stage of labour. No further drugs were administered thereafter.

Arterial pressure, heart rate and ventilation rate were measured every 5 min for 30 min and, thereafter, at 15-min intervals or when clinically indicated. Maternal Pa_{CO_2} was measured in only four patients because of the inconvenience of arterial blood sampling in this setting.

Assessment of pain

The severity of pain was assessed every 5 min during the first 30 min, and at 15-min intervals thereafter, using a numerical rating scale 0–10 (0 = no pain at all, 10 = worst possible pain). Recurrence of pain was considered significant when the new pain score was equal to or greater than 50% of the initial pain score. At that moment, a new bimanual vaginal examination was carried out to obtain information regarding the descent of the fetal head (ischial spine = 0) and the rate of cervical dilatation (table II).

Assessment of the newborn

The newborn infants were assessed using the Apgar score at 1, 3, 5 and 10 min and the Amiel-Tison score at 15–30 min of life (Amiel-Tison, Barrier and Shnider, 1982). The same neurobehavioural tests were performed on the 16 newborns which served as controls.

Comparisons between the groups were analysed using the Kruskal–Wallis one-way analysis of variance. In six patients, maternal blood samples were taken at birth, together with arterial and venous blood samples from the umbilical cord to permit the measurement of alfentanil concentration (radioimmunoassay).

RESULTS

Patient characteristics

The two groups were comparable with regard to maternal age and the duration of gestation (table I). The higher mean Bishop score in the control group can explain the shorter total duration of labour (Friedman et al., 1966).

Pain scores

The mean initial pain score was somewhat higher than we usually observe and this was probably because of the score of 9 given by two patients.

Pain relief was excellent within less than 5 min

TABLE I. *Patient data (mean (range)).*

	Control group		Alfentanil group	
Number of patients	16		16	
Maternal age (yr)	25.79	(22–34)	25.85	(22–33)
Duration of gestation (weeks)	40.10	(39–41)	39.80	(38–42)
Dilatation at time of extradural (cm)		—	3.4	(1–6)
Bishop score*	6.8	(4–9)	5.25	(3–9)
Duration Phase I + Phase II (min)	401.25	(210–600)	612	(265–925)

* Bishop score = measure of inducibility of labour.
Recorded at the moment the patient was included in the study.
Includes evaluation of:

Station of the presenting part	−3	−2	−1/0	+1/+2
Dilatation (cm)	0	1–2	3–4	> 5
Effacement (cm)	> 2.5	2	1	< 0.5
Consistency	Firm	Medium	Weak	—
Position of os	Post.	Central	Anterior	—
Rated as.	0	1	2	3

(Maximum = 13 patients)

TABLE II. *Pain scores. * Pain considered significant if score $\geqslant$ 50 % of initial pain score. † Sum of the amplitudes (in mm Hg) of the contractions occurring during a 10-min period: a = before pain recurrence; b = when new significant pain score was recorded. ‡ No intrauterine pressure monitoring. § Patient 14: no pain recurrence (according to our criterion)*

Patient No.	Initial pain score	Recurrence of pain*		Position (Ischial spine=0)	Dilatation (cm)	Montevideo units†	
		Interval (min)	Score			a	b
1	9	180	6	0	6	120	175
2	7	120	4	−1	8	‡	
3	7	120	5	?	6	‡	
4	8	180	4	0	4	‡	
5	5	160	4	−1/0	7	150	200
6	8	180	6	0	6	120	210
7	7	150	4	−2	5	100	270
8	7	240	4	−2	5	110	170
9	6	240	5	−1	5	130	170
10	8	240	5	0	9	170	190
11	8	180	4	0/+1	10	‡	
12	6	180	4	−1	4	‡	
13	9	270	5	−1	6–7	100	185
14	8	—§	—	—	—		
15	6	180	4	−2	4	125	160
16	8	180	6	−2	4	170	250
Range	5–9	120–270	4–6	−2→0	4–10		

in all patients and remained acceptable for 2–4.5 h (fig. 1).

No correlation could be found between the recurrence of pain (as defined above) and the degree of cervical dilatation, nor with the descent of the fetal head. However, recurrence of pain did coincide with an increase in uterine activity as expressed by the increase in Montevideo Units (table II). Satisfactory pain relief could be maintained in 11 of the 16 patients by injecting additional doses of alfentanil. Such supplements of alfentanil only helped when given early in labour; they did not provide adequate analgesia in the latter part of stage I. Five patients required supplements of extradural bupivacaine.

Alfentanil requirements

The wide range observed in total dose is explained by both considerable differences in the duration of the infusions and in the body weight of the patients (50–105 kg), and the several supplementary doses given to some patients (table III).

Maternal and neonatal plasma concentrations of alfentanil at birth

No correlation was found between the duration of stage II—the interval during which no alfentanil was given—and the neonatal plasma concentrations of alfentanil. The umbilical vein: umbilical artery ratio of alfentanil was greater than 1, denoting fetal uptake or metabolism, or both (table IV).

Clinical effects and side-effects

Drowsiness was reported by almost half the patients and occurred within 1–2 min of the injection (table V). However, cerebral cognitive functions remained normal throughout labour. Dizziness occurred in three patients but only within the first 15 min of the injection. Itching, confined to the abdomen and legs, was reported by almost all patients, but elicited no spontaneous complaints. The incidence of nausea, excluding one patient receiving $PGF_{2}\alpha$, was 27%. No urinary retention was observed in 10 patients; information regarding the other six patients was unavailable. Hypotension, defined as a decrease in systolic arterial pressure of greater than 10%, did not occur. Ventilation rate decreased significantly from preinjection values, but this could be

TABLE III. *Alfentanil requirements (mean (range))*

Duration of infusion (min)	299.3 (110–520)
Time from stopping infusion to delivery (min)	38.7 (16–68)
Total dose (mg)	13.3 (6.4–20.9)
Total dose (μg kg^{-1})	198.8 (54.4–334.7)
Total dose (μg kg^{-1} h^{-1})	38.1 (27.9–49.5)

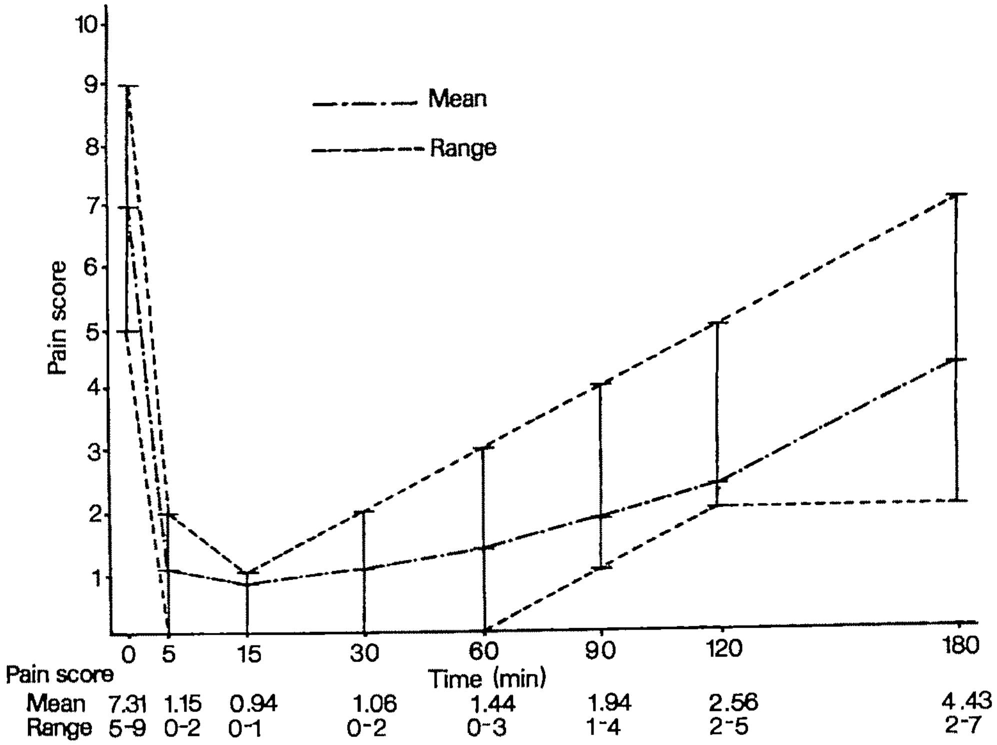

FIG. 1. Pain score (mean and range) *v.* time.

attributed to the effective analgesia and was never less than 15 b.p.m. In four patients, arterial blood samples, drawn when analgesia was complete, revealed Pa_{CO_2} values between 4.3 and 4.7 kPa—within the normal range for the parturient.

Evaluation of the neonate

As expected, theoretically, the duration of stage II was not prolonged in the alfentanil group compared with the control group. All the newborn infants had Apgar scores of 7 or more at 1 min (table VI). One baby in the control group had Apgar scores of 1, 3 and 5 at 1, 5 and 10 min and this accounted for the lower mean Apgar score in the control group. Umbilical arterial and venous pH values were comparable in both groups.

The total score on the neurological part of the Amiel–Tison test was significantly lower in the alfentanil group. This resulted from a lower score for passive (6.07) and active tone (5.75) than those recorded in the control group (passive: 7.31; active: 7.63). Further evaluation of the neonates by the paediatrician did not denote any abnormal feeding habits nor behavioural changes.

TABLE IV. *Maternal and neonatal plasma concentration of alfentanil at birth*

Patient No.	Duration of stage II (min)	Maternal concn (ng ml^{-1})	Umb. vein (ng ml^{-1})	Umb. art. (ng ml^{-1})	Umb. vein to maternal ratio
1	35	39.1	12.8	—	0.327
2	35	27.3	7.36	—	0.27
3	20	21.5	4.75	4.11	0.221
4	30	29.4	8.07	6.44	0.274
5	50	28.3	16.3	11.3	0.576
6	30	47.7	16.2	—	0.339

TABLE V. *Side effects.* † *Excluding one patient who received* $PGF_2\alpha$

	No.	%
Drowsiness	7/16	43.75
Dizziness	3/16	18.75
Nausea/vomiting	5/16	31
	4/15	27†
Itching	15/16	94
Urinary retention	0/10	
Hypotension	0/16	

DISCUSSION

The continuous extradural infusion of alfentanil was chosen for conduction analgesia during labour because of the short elimination half-life of alfentanil (Bower and Hull, 1982), and on account of the short duration of action of a single injection of the drug (preliminary trial). These facts, together with the low umbilical cord:maternal vein ratio of 0.3 (Bonnardot, 1983), led us to believe that the administration of additional doses, when required, would not increase the likelihood of neonatal ventilatory depression.

Excellent pain relief was invariably obtained within 5 min after the injection of the loading dose of alfentanil; its high lipid solubility favoured rapid penetration of the dura. However, vascular uptake and transport via the posterior radicular artery or excretion through the arachnoid granulations in the dural cuff regions, or both, are important coexisting mechanisms (Cousins and Mather, 1984).

Two characteristics of the pattern of pain relief in this study were of interest. First, no relationship could be found between the recurrence of pain and the position of the presenting part, or with the degree of cervical dilatation. This eliminated the possibility that recurrent abdominal (not perineal) pain, could be caused by central pain transmission via non-blocked nerves. On the other hand, there was a positive correlation, with an increase in Montevideo units or, in other words, with an increase in the contractile force of the uterus.

Second, it was noted that the incremental doses resulted in transient improvements in analgesia when given fairly early in labour, and not at all when given late in the first stage of labour. The same phenomenon was seen in the preliminary trial when the loading dose was given late in stage one; pain relief remained inadequate even when alfentanil 90 $\mu g\ kg^{-1}$ was given. This indicated that there is an inherent maximal analgesic capacity for extradurally administered alfentanil; thus, when uterine activity exceeds a certain limit in any individual patient, the administration of alfentanil, in whatever dose, will not result in adequate pain relief. Other studies (Carrie, O'Sullivan and Seegobin, 1981; Justins, Francis and Houlton, 1982; Justins, Knott and Luthman, 1983) demonstrated invariably the poor efficacy of extradural opioids during late stage I and during

TABLE VI. *Evaluation of the neonate.* † *Mean (range)*; ‡ *mean (SD).* § *One control patient with Apgar scores 1, 3 and 5 at 1, 5 and 10 min.* ¶ *Amiel-Tison Score: adaptive capacity score omitted.* **** $P < 0.005$; *** $P < 0.001$

	Control group	Alfentanil group
Time amniotomy to delivery (min)	401.25 (210–600)†	612 (265–925)
Duration second stage (min)	33.63 (5–90)†	29.62 (15–68)
Apgar score		
1 min	8.21§ (1–10)†	8.56 (7–10)
3 min	9.47 (3–10)	9.60 (8–10)
5 min	9.75 (5–10)	9.80 (9–10)
pH		
Venous	7.312 (7.15–7.37)†	7.32 (7.19–7.39)
Arterial	7.284 (7.11–7.35)	7.25 (7.12–7.38)
Amiel-Tison score¶		
Passive tone (max. 8)	7.31 ± 0.20‡	6.07 ± 0.25****
Active tone (max. 10)	7.63 ± 0.20	5.75 ± 0.52***
Primary reflexes (max. 6)	5.50 ± 0.13	5.07 ± 0.18
General assessment (max. 6)	5.63 ± 0.15	5.87 ± 0.13
Total score (max. 30)	26.06 ± 0.34‡	22.92 ± 0.68****

the second stage of labour. However, as supplementary doses were not administered, the possibility remained that an inadequate dose of opioid had been given in the first place. Our findings refute this possibility. It has been established that extradurally administered opioids exert their analgesic effect through a direct action upon the dorsal column and not centrally through intrathecal spread or vascular absorption (Kitahata and Collins, 1981; Yaksh, 1981). Side-effects, however, are caused by the systemic absorption of the opioid. The rapid onset of such effects seemed to indicate a relatively rapid uptake of the drug via the extradural venous plexus.

Sedation was found to occur even before the onset of analgesia and to last throughout the period of the continuous infusion of alfentanil, although this effect was less apparent as analgesia became less complete. The lack of impairment of maternal cerebral function and the absence of complaints from the patients made us believe this side-effect was readily acceptable.

The high incidence of nausea and vomiting was disappointing and probably resulted from the direct effect of alfentanil on the area postrema in the floor of the fourth ventricle. In two patients, small doses of naloxone were administered to abolish the vomiting. As analgesia remained unaffected, this observation supports the hypothesis that the analgesia attributable to alfentanil results from an extradural, and not a central, site of action.

Itching has been reported to be frequent in parturient women (Scott, Bowen and Cartwright, 1980). Mild pruritis was reported by 15 of the 16 patients in this study, but only on direct questioning. This sensation was confined to the abdomen and legs and was not consistent with the usual finding of most severe itching in the palate and the face (Yaksh, 1981). Facial itching occurred in two patients immediately after the administration of a "top-up" dose.

Although adequate Apgar scores were found in the alfentanil group, the Amiel-Tison test clearly demonstrated neonatal hypotonia. As this was not reflected by the Apgar score, the evaluation of the effects of intrathecal and extradural opioids during labour should include the more sensitive neurobehavioural tests. Neonatal hypotonia constituted one of the major, if not the major, drawback of the use of alfentanil as it could lead to serious problems if other compromising factors were present.

The failure of opioid analgesia during the late stage I and stage II of labour could be caused by the transmission of pain via high-threshold neurones in lamina I which do not project on deeper laminae, but directly into the spinothalamic tract, thus bypassing the opioid μ-receptors concentrated in the substantia gelatinosa (Bowsher, 1978; Yaksh, 1981).

Alternatively, the observation that such different products as serotonin (Yaksh, 1978), baclofen (Yaksh, 1978) and midazolam (Whitwam, 1983) can produce spinal analgesia, suggests that there are definite spinal systems mediating nociception, on which opioids cannot exert any influence.

It may be that "selective spinal analgesia" during labour is "too selective" and that a combination of an opioid with a local anaesthetic agent will be necessary.

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EFFECT OF GRAVITY ON THE SPREAD OF EXTRADURAL ANAESTHESIA FOR CAESAREAN SECTION

M. C. NORRIS AND D. M. DEWAN

SUMMARY

The effect of gravity on the spread of extradural anaesthesia was evaluated in a series of parturients undergoing elective Caesarean section. Following placement of an extradural catheter, 25 patients were placed 30–40° head-up for 20 min during the administration of the local anaesthetic drug; 25 additional patients remained supine during injection. Extradural anaesthesia was induced with 3% 2-chloroprocaine 23 ml and analgesia to pinprick assessed at 5-min intervals. Additional drug was given after 20 min, if required. There were no differences in the rate of onset of sacral blockade or in the extent of neural blockade between the two groups. The semi-upright position was not necessary to ensure adequate sacral anaesthesia for Caesarean section.

Extradural anaesthesia for Caesarean section should provide blockade of the sacral nerve roots (Thorburn and Moir, 1980). Some authors utilize gravity to encourage the sacral spread of local anaesthetic drug in the extradural space, and recommend that blockade be induced in the sitting (Bromage, 1978; Thorburn and Moir, 1980) or semi-sitting (Datta et al., 1979; Crawford, 1980) position. Others believe that the effects of gravity are minimal, and establish anaesthesia while the patient is supine (Bonica, 1980; Writer, Dewan and James, 1984). Although the relationship between gravity and the spread of extradural analgesia during labour has been studied previously (Merry et al., 1983; Rickford and Reynolds, 1983), the present authors are unaware of any controlled studies comparing the influence of the position of the patient on the adequacy of sacral blockade in association with Caesarean section. In this study, the effects of gravity on the onset and extent of sacral anaesthesia in parturients undergoing elective Caesarean section were examined.

PATIENTS AND METHODS

The Clinical Research Practices Committee approved the design of the study, and 50 patients, (ASA I and II) at term, receiving extradural anaesthesia for elective Caesarean section participated in the study. All patients were premedicated with 30 ml of sodium citrate 0.3 mol litre^{-1}. An i.v. cannula was placed and the patients assumed the lateral position. An extradural catheter was inserted at the L2–3 or L3–4 space with a maximum of 4 cm of catheter in the extradural space. All patients received in i.v. infusion of 1–2 litre of lactated Ringer's solution during the establishment of blockade. The patients were allocated randomly to two groups. Patients in one group ($n = 25$) remained supine throughout the induction of the extradural anaesthesia while those in the other ($n = 25$) were placed in a 30–40° head-up position. Anaesthesia was induced using 3% 2-chloroprocaine and a standardized technique (Writer, Dewan and James, 1984). At time 0, 3 ml was injected and the patient observed for 5 min for signs of intrathecal injection. In the absence of symptoms, 5 ml was injected and the patient asked about tinnitus and circumoral paraesthesiae to exclude intravascular placement. One minute later if there were no symptoms suggesting i.v. injection, an additional 15 ml was administered. Additional drug was given after 20 min, if required. Maternal arterial pressure and heart rate, as well as the level of analgesia to pinprick, were recorded at 5-min intervals for 30 min. All patients had left lateral tilt maintained throughout the study. Any decrease in maternal

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systolic pressure was treated by increasing the rate of fluid administration. If the arterial pressure did not respond promptly and decreased to less than 70% of control, ephedrine 5–10 mg was administered i.v. and repeated as necessary. When an adequate level of anaesthesia was attained, the patients were transported to the operating suite and transferred to the operating table. Induction to skin incision, induction to delivery and uterine incision to delivery intervals were recorded. At delivery, umbilical arterial and venous blood was sampled from a doubly clamped section of umbilical cord. A paediatrician unaware of this study assigned the Apgar scores.

All data are expressed as mean ± SEM. Maternal arterial pressure and heart rate were analysed using an analysis of variance for repeated measures. Patient data, delivery intervals and umbilical blood-gas tensions were analysed with the Student's *t* test and the level of analgesia and Apgar scores were analysed using the Chi-square test.

RESULTS

Maternal age, weight and height did not differ between the groups (table I). Three patients were withdrawn from the study: two developed unilateral blockade, and in one case, the surgeon was delayed and the operation postponed. All patients had satisfactory sensory blockade and no patient required general anaesthesia. Three patients in the supine group and one in the upright group complained of discomfort with peritoneal manipulation and required nitrous oxide (30–40%) supplementation before delivery. Opioids and sedation were administered after delivery at the discretion of the attending anaesthetist. Twenty subjects in each group required only the initial 690 mg of 2-chloroprocaine to provide adequate blockade. Five patients in each group received additional local anaesthetic. The supine patients required a mean dose of 705.6 ± 10.4 mg, while the patients in the upright group required 720.0 ± 12.2 mg (ns). The time to establish adequate blockade (induction to skin incision) was similar in both groups, as were the induction to delivery and uterine incision to delivery intervals (table I).

TABLE I. *Characteristics of patients (mean ± SEM)*

	Group A (Supine)	Group B (Upright)
Age (yr)	29.5 ± 0.9	27.8 ± 0.8
Weight (kg)	78.8 ± 3.5	73.4 ± 2.2
Height (cm)	161.8 ± 1.1	161.5 ± 1.2
Total dose of 2-chloroprocaine (mg)	705.6 ± 10.4	720.0 ± 12.2
Induction to skin incision (min)	39.4 ± 1.2	41.9 ± 1.1
Induction to delivery (min)	48.4 ± 1.4	50.5 ± 1.4
Uterine incision to delivery (s)	92.5 ± 7.6	104.1 ± 12.4

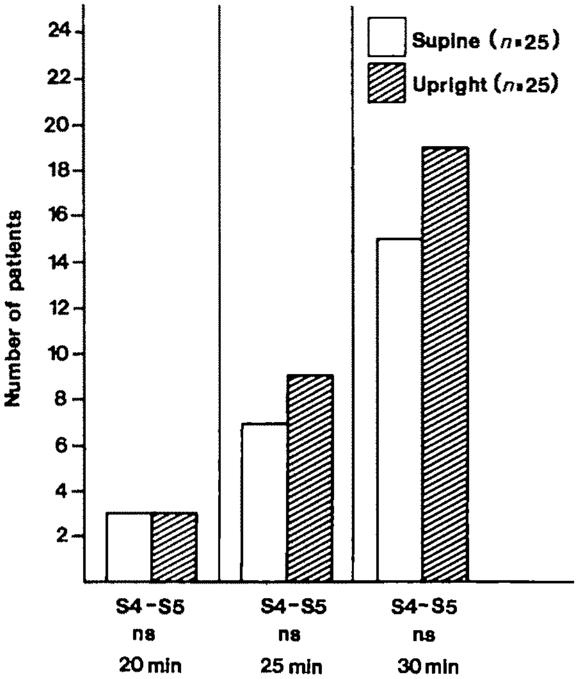

FIG. 1. Number of patients having analgesia extending to the S4 or S5 dermatome at 20, 25 or 30 min. Twenty-five patients remained supine while 25 patients were placed 30–40° head-up for 20 min during induction of anaesthesia.

There were no differences between the groups in the onset of sacral blockade (fig. 1). By 30 min, 15 of 25 patients in the supine group and 19 of 25 in the upright group had a level of analgesia to pinprick extending caudally to the S4 or S5 dermatome. By the time of skin incision (40 min) all patients had analgesia extending to the S4–S5 dermatomes. Cephalad spread of analgesia was significantly greater in the supine group at 20 min, but by 30 min, cephalad spread was similar in both groups (fig. 2).

The incidence of hypotension was the same in both groups. Fourteen of 25 patients in the supine group required ephedrine 29.3 ± 5.5 mg (range

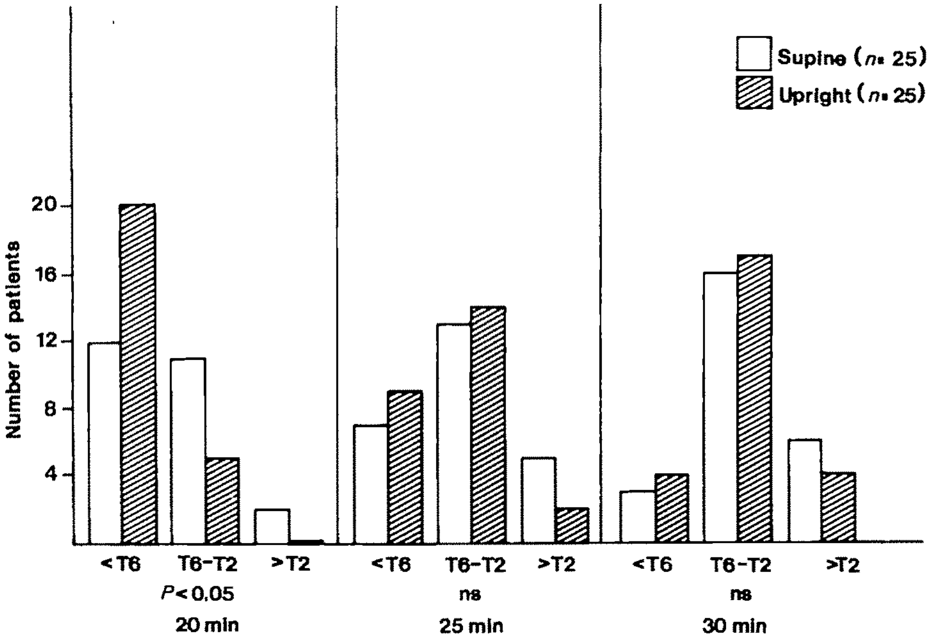

FIG. 2. Cephalad spread of analgesia to pinprick. Groups as in figure 1.

5–90 mg), while 15 of 25 patients in the upright group required ephedrine 30.1 ± 8.6 mg (range 10–120 mg) (ns). Fetal outcome, as assessed by umbilical blood-gas tensions and Apgar scores, was satisfactory in both groups.

DISCUSSION

Satisfactory extradural anaesthesia for Caesarean section requires bilateral sensory blockade from S5 to at least T6. Extraction of the fetal head and traction on the uterus stimulate the sacral nerves and, without adequate sensory blockade, pain occurs (Thorburn and Moir, 1980). Many believe gravity influences the distribution of extradural anaesthesia. Thorburn and Moir (1980), using bupivacaine, and Bromage (1978), using bupivacaine, lignocaine or etidocaine advocated that anaesthesia be induced with the patient in the sitting position, and that this be maintained for 10 min following injection. Crawford (1980) and Datta and colleagues (1979), both using bupivacaine, placed patients in a semi-sitting position for at least 10 min. However, Writer, Dewan and James (1984), using 2-chloroprocaine, achieved satisfactory anaesthesia with the patient in the supine position. We found no difference in the onset and extent of sacral blockade in patients placed in the semi-upright position as compared with those who remained supine. Similar findings were reported by Merry and co-workers (1983) studying bupivacaine analgesia during labour. They reported that the sitting position may actually inhibit caudal spread of local anaesthetic drug. Although cephalad spread of analgesia was more rapid in the supine position, the ultimate cephalad extent of blockade was the same in both groups. This more rapid cephalad spread of blockade conferred no clinical advantage to the supine position, as up to 40 min was still required for the development of adequate sacral analgesia. Hodgkinson and Husain (1981) found that gravity had no influence on the final cephalad spread of blockade in non-obese parturients for Caesarean section.

The apparent lack of effect of gravity on the spread of analgesia found in this study may be attributable to several factors. Large volumes of anaesthetic solution (23 ml) may fill the extradural space regardless of the position of the patient. Twenty millilitre of contrast medium easily spreads to mid-thoracic levels in the non-pregnant patient (Burn, Guyer and Langdon, 1973). With pregnancy there is engorgement of the extradural veins and a consequent decrease in the size of the extradural space (Bromage, 1978). Many of our patients complained of transient nuchal discomfort during the injection of the drug, suggesting significant distension of the upper thoracic extradural space. Grundy and associates (1978) believe that fluids injected to the extradural space flow along with the path of "least resistance". In the upright position, gravity causes dependent pooling of cerebrospinal fluid and blood which may occlude the lumbar and sacral extradural space and solutions would actually tend to spread in a cephalad direction (Nishimura, Kitahara and Kusakabe, 1959). Studies of radio-labelled local anaesthetic drugs (Nishimura, Kitahara and Kusakabe, 1959) and contrast media (Burn, Guyer and Langdon, 1973) injected to the extradural space showed similar caudad and cephalad spread in both the upright or supine position. Finally, the extent of neural blockade is only broadly related to physical spread of the local anaesthetic drug (Burn, Guyer and Langdon, 1973). The eventual extent of blockade also depends on the diffusion of drug into the neuraxis along concentration gradients (Bromage, 1978).

Although 2-chloroprocaine was used in this study, use of other local anaesthetic drugs in similar volumes would probably produce the same results. Indeed, in our clinical experience with 0.5% bupivacaine, adequate sacral blockade is produced in the supine position.

Hypotension is a common side effect of extensive extradural anaesthesia and the upright position could increase its incidence. However, in this study, patients had adequate uterine displacement and received generous crystalloid infusions i.v. before the induction of anaesthesia. The incidence of hypotension was similar in the two groups. Any decreases in arterial pressure of more than 30% from control were promptly treated with ephedrine, and neonatal outcome was good in both groups.

In conclusion, in this series of patients, the upright position was not necessary to ensure adequate sacral anaesthesia. The quality of anaesthesia, maternal haemodynamics and fetal outcome were similar irrespective of position.

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EFFECT OF POSTURE DURING THE INDUCTION OF SUBARACHNOID ANALGESIA FOR CAESAREAN SECTION

Right v. *Left Lateral*

I. F. RUSSELL

SUMMARY

Thirty-five women scheduled for elective Caesarean section were randomly assigned to have subarachnoid analgesia induced in either the right or left lateral position. They were then turned supine with a wedge under the right hip. No patient in the right-sided group required further analgesia. Five patients in the left-sided group required postural manipulation to encourage the spread of analgesia and two required supplementary analgesia ($P < 0.01$).

Subarachnoid analgesia is gaining popularity in many branches of anaesthetic practice. Its use in obstetrics was encouraged by Crawford (1984) for those situations where the alternative is general anaesthesia. However, Crawford (1984) did not advocate its use for Caesarean section because of the risk of arterial hypotension and the incidence of inadequate analgesia—which necessitates subsequent general anaesthesia. Shnider (1973), for example, quoted that 10% of patients required a superimposed general anaesthetic and that a further 55% required some form of supplementary analgesia. More recent evidence suggested the likely reason for this is that the dose of amethocaine advocated for Caesarean section in America was inadequate (Chantigian et al., 1984). On the other hand the greater use of subarachnoid analgesia for Caesarean section has been advocated (Brownridge, 1981; Abouleish and Bourke, 1984; Moore and Batra, 1984), especially if no extradural catheter is in place, because of its speed of onset and absence of any risk of toxicity. If this advice is to be followed, it is essential that adequate analgesia should be provided and, in this context, the posture of the patient during and immediately after the induction of subarachnoid analgesia may be important. Sprague (1976) drew attention to the importance of technique and pointed out that the induction of subarachnoid analgesia in the left lateral position followed by the supine left semi-lateral position (a wedge under the right hip) gave very poor spread of analgesia, and he abandoned this posture in his study when three out of four patients required general anaesthesia to permit the completion of surgery. No such problems were encountered with induction in the right lateral position. Personal observations over 10 yr suggest that the left lateral is the position in which patients are placed most commonly during the performance of subarachnoid analgesia for Caesarean section, and this may be a possible reason for the poor results. Although Sprague (1976) gave no explanation for the different pattern of analgesia in the two groups, an effect of gravity on the heavy amethocaine was implied.

Recently, it has been suggested that posture, independent of gravity, can influence vertebral venous volume and thus affect the dermatomal spread of analgesia (Russell, 1983, 1984). More significant caval occlusion seems likely when turning from the right lateral to the left semi-lateral position than would occur when turning to this position from the left lateral position. If this is so, it should be possible to detect a difference in the behaviour of an isobaric solution placed in the subarachnoid space, depending on the original position of the patient during the actual intrathecal injection. Also, by using an essentially isobaric solution, any significant effect of gravity could be excluded.

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Although it is accepted that 0.75% plain bupivacaine may be slightly hypobaric in relation to CSF at body temperature, the effect of this hypobaricity is likely to be minimal in the horizontal position (Scott and Sinclair, 1982). For those who do not accept this lack of gravitational effects, the hypobaric tendency would tend to restrict the cranial spread of analgesia both during induction (hips are said to be wider than shoulders in the female (Greene, 1985)), and while lying supine on a wedge.

PATIENTS AND METHODS

The 35 patients who are the subject of this report form a part of a larger group, 80 in all, in whom subarachnoid analgesia was induced with volumes of 0.75% bupivacaine varying from 1.0 to 2.0 ml before the drug was withdrawn for use in obstetric anaesthesia. These 35 patients formed the largest homogeneous group in that they all received 1.5 ml, and all were undergoing an elective Caesarean section within 2 weeks of term. The women were randomly assigned to have subarachnoid analgesia induced in either the right or the left lateral position.

Following the injection of 0.75% plain bupivacaine 1.5 ml through a 25-gauge needle at L2–3, the patients were immediately turned supine and a wedge was placed under the right hip. Analgesia to pin prick was assessed bilaterally at 2, 5, 10, 15, 20 and 30 min. Analgesia was defined as loss of pin-prick sensation.

An i.v. fluid preload was administered immediately before induction. This consisted of either Hartmann's solution 2 litre or Hartmann 1 litre plus Haemaccel 0.5 litre. Oxygen 6 litre min^{-1} was administered via a Hudson mask, until delivery of the baby. After delivery, supplementary analgesia was provided via this mask when required (oxygen 2 litre min^{-1}, nitrous oxide 6 litre min^{-1} and trichloroethylene, as necessary). Verbal contact with the patient was maintained at all times.

At 10 min, if the upper level of analgesia was T10 or below and had extended by less than two segments from the 5-min assessment, the wedge was removed and the patient rolled slowly from a right- to a left-tilted position several times before being repositioned on the wedge (postural manipulation).

The author worked single-handed throughout this study and was aware of the position of the patient during induction.

RESULTS

Seventeen women had subarachnoid analgesia induced while lying on their left side initially (group L); 18 women had subarachnoid analgesia induced while lying on their right side initially (group R). One patient from each group was excluded from the final analysis because of technical difficulties during the performance of the block, in that no free flow of CSF was obtained. Subsequent analgesia in these two patients was very limited. One of these patients had spinal analgesia induced successfully via another interspace and gave no further problems. The other patient received a successful extradural following a second "dry" tap.

Student's *t* test for unpaired data revealed no significant difference between the mean analgesic levels of the remaining patients in the two groups at any time (table I). However, in group L, five patients required postural manipulation. This resulted in a sudden rapid extension of a previously static or slowly extending blockade. One of these patients, and one other from group L, subsequently required supplementary analgesia. No patient from group R required either postural manipulation or supplementary analgesia ($P < 0.01$). Table II shows the difference in mean segmental levels of analgesia between the five patients requiring postural manipulation and the rest of group L. These differences were significant.

The incidence of hypotension was the same in both groups (50%), although this was always short lived and responded rapidly to ephedrine 5–15 mg i.v.

Seven patients (20%) developed post-spinal

TABLE I. *Mean segmental levels of analgesia (±standard deviation) found in the two groups of women having subarachnoid analgesia induced with 0.75% plain bupivacaine 1.5 ml There was no significant difference between the two groups at any stage (Student's* t *test)*

Time (min)	Right side	Left side
2	T10.7 (±1.9)	T10.3 (±4.2)
5	T7.4 (±3.1)	T6.8 (±4.8)
10	T4.9 (±3.4)	T5.1 (±5.4)
15	T3.0 (±2.6)	T2.8 (±3.9)
20	T2.5 (±2.5)	T1.8 (±2.7)
30	T2.4 (±2.6)	T1.8 (±2.7)

TABLE II. *Mean segmental levels of analgesia (±standard deviation) found in women having subarachnoid analgesia induced with 0.75% plain bupivacaine 1.5ml, lying on their left side initially. The "intervention" group required postural manipulation (PM) at 10 min* to encourage the spread of analgesia. The "no intervention" group did not require manipulation. The significance of the difference in analgesic levels between these two sub-groups is also shown* (*Student's* t *test*)

Time (min)	Intervention (PM) ($n=5$)	No intervention ($n=11$)	P
2	L2 (±2.5)	T8.6 (±3.7)	< 0.05
5	T12.2 (±2.4)	T4.3 (±3.2)	< 0.001
10	T10.8 (±3.2)*	T2.0 (±3.6)	< 0.001
15	T6.4 (±3.3)	T1.2 (±3.0)	< 0.01
20	T3.4 (±0.6)	T1.1 (±3.0)	< 0.05
30	T3.4 (±0.5)	T1.1 (±3.0)	< 0.05

headaches (four in group R; three in group L). Three of these were readily relieved by paracetamol by mouth; four (11%) were given a blood patch.

DISCUSSION

These results support Sprague's (1976) findings that for Caesarean section with the patient in a left semi-lateral position, the spread of analgesia is enhanced if the subarachnoid injection is made while the patient lies in the right lateral position. Although only two patients (not statistically significant) in group L required supplementary analgesia, this number would undoubtedly have been much greater had postural manipulation not been used. This supposition is based on the fact that, at 10 min, analgesia was within three segments of its highest level in the remaining 28 patients and within two segments in 22 of these. Thus, without intervention, the five patients in group L who were subjected to postural manipulation may only have achieved a final level of T7/8, which in most cases would be inadequate for Caesarean section. It would have been scientifically more correct to have left these patients alone and to have observed the total undisturbed spread of analgesia, but it is doubtful if this would have been ethically justifiable, since it was already evident that the spread of analgesia was reduced.

The limited spread of analgesia in the five patients is unlikely to be a gravitational effect since, in all probability, gravity has no clinically discernible effect on isobaric or hypobaric solutions while the patient is in a horizontal position (Scott and Sinclair, 1982). A more likely reason is the avoidance of any significant caval occlusion in this sub-group, since none developed hypotension before postural manipulation, although the absence of hypotension may only reflect the restricted degree of blockade.

If the restricted blocks were attributable to gravitational effects, then this merely emphasizes the importance of postural manipulation in causing the analgesic levels to extend against the effects of gravity.

Despite the hypothesis that the induction of subarachnoid anaesthesia in the left lateral position may limit spread, there were no significant differences in the mean analgesic levels between groups R and L, although one short patient (4 ft 11″; 151 cm) in group L achieved total analgesia to pin prick up to C2 with no ventilatory embarrassment or weakness of the arms (she could only feel pin prick on her face).

It has been suggested that changes in venous pressure associated with changes in posture are unlikely to be the cause of the facilitated spread of subarachnoid drugs during pregnancy (Marx, Zematis and Orkin, 1961; Shah, 1984). However, the relationship between CSF pressure and venous pressure may be complicated by reciprocal volume changes within the different compartments and neither author considered that a greater increase in CSF pressure in the pregnant patient may have been prevented by compensatory displacement of CSF in a cranial direction with a complementary decrease in vertebral venous volume above the level of the vena caval obstruction.

The importance of venous pressure was emphasized by Barclay, Renegar and Nelson (1968), who showed that the spread of subarachnoid analgesia is related to femoral venous pressure. High segmental levels of analgesia could be obtained in non-pregnant subjects by inflating an abdominal binder until the femoral venous pressure of the non-pregnant patient was the same as the mean pressure found in a group of pregnant patients (Barclay, Renegar and Nelson, 1968). There is also a marked difference in the behaviour of previously stable analgesic levels between pregnant and non-pregnant subjects turned from the lateral to the supine position. With patients in a lateral position, 0.5% plain bupivacaine 3.0 ml produced a stable level of T11 and T10 in non-pregnant and pregnant patients, respectively, but on being placed supine the non-pregnant group had a mean analgesic level of T8 only, while the analgesic levels in the supine pregnant group rose to a mean of T3 (Russell, 1983, 1984).

The only way this rapid rise in analgesic levels can be explained is by some kind of physical displacement of the anaesthetic agent. In the present study it would appear that, at least in some patients, this physical displacement is decreased when turning from the left lateral to the supine left tilt position. This would fit in with a vena caval occlusion hypothesis, since turning from the left lateral to the left semi-lateral tilted position always tends to leave the uterus lagging behind to the left, thus minimizing caval occlusion. Turning from the right lateral, however, results in the uterus tending to lie on the vena cava until it is displaced by insertion of the wedge under the left hip.

The mean levels of analgesia obtained in this study were similar to those observed in a previous study (Russell, 1983) using 0.5% plain bupivacaine 3.0 ml, and are similar to as yet unpublished results using 2–2.5 ml of 0.5% bupivacaine in dextrose. These high levels may cause anxiety to many anaesthetists, but (apart from transient and easily treatable hypotension) appear to be necessary to achieve satisfactory analgesia and to allow certain forms of surgical manipulation such as the routine insertion of bilateral abdominal packs by one obstetrician or the occasional delivery of the uterus onto the abdominal wall—when little if any change in maternal arterial pressure or heart rate occurs. Interestingly, the unpublished results of the remaining 55 patients reveal no significant differences between the highest mean levels of analgesia obtained with 2.0 ml, 1.5 ml or 1.0 ml, although four of the seven patients receiving 1.0 ml required supplementary analgesia and two of these had general anaesthesia induced to allow the completion of surgery. Two of the 1.0 ml group also became hypotensive (29%). This small volume was abandoned after the second general anaesthetic.

The high incidence of hypotension (50%) was similar to that observed in other studies (Russell, 1983), but deserves comment. Hypotension is a recognized complication of subarachnoid analgesia and, although its incidence is high in this study, it can be reduced markedly by the use of i.v. ephedrine at the first sign of a decrease in arterial pressure, or by the prophylactic use of ephedrine (Kang, Abouleish and Caritis, 1982). Prolonged hypotension with a reduction in uteroplacental blood flow will inevitably result in fetal acidosis. Since in this investigation the hypotension was always of short duration, and all infants had high Apgar scores, with times to sustained ventilation well below 60 s, fetal blood-gas tensions were not measured.

The incidence of headaches (20%) was disappointing, but it is similar to that noted in previous studies on young women (Chambers, Edstrom and Scott, 1981; Russell, 1983), with about half of these receiving an extradural blood patch. This is certainly the biggest drawback to the widespread acceptance of subarachnoid anaesthesia for Caesarean section. Some authors do not seem to have this problem with their obstetric patients (Brownridge, 1981). Others, presumably because of the low incidence, do not mention it (Chantigian et al., 1984). Why there is such variation in the incidence of headaches is not clear, but it is possible that the use of a 26-gauge needle may result in a lower incidence of post-spinal headaches (Carrie, personal communication).

While delay in the treatment of hypotension and the problem of post-spinal headaches limit the use of the technique as described, the results do support Sprague's (1976) findings that the posture of the patient during the subarachoid injection has a significant effect on the adequacy of the resultant analgesia. The effect of postural manipulation in encouraging the spread of analgesia should also be noted.

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SUBARACHNOID ANALGESIA FOR CAESAREAN SECTION.

A Double-Blind Comparison of Plain and Hyperbaric 0.5% Bupivacaine

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SUMMARY

Equal volumes (2.5 ml, 12.5 mg) of plain 0.5% bupivacaine (glucose-free) and hyperbaric 0.5% bupivacaine (in 8% glucose) were compared in a randomized double-blind study of 40 patients undergoing Caesarean section under subarachnoid anaesthesia. There were no differences in the rate of onset, maximum spread, number of patients with high cervical levels, duration of anaesthesia or incidence of post-spinal headaches between the two solutions. The median maximum cephalad levels of analgesia were (hyperbaric) T1 (range C1–T4), and (plain) T2 (range C1–T4). Thirteen patients in the hyperbaric group and 10 in the isobaric group required i.v. ephedrine to treat hypotension. Nine patients (23%) developed a post-spinal headache, and three were treated with an extradural blood patch.

The addition of 0.5% hyperbaric bupivacaine (0.5% bupivacaine in 8% dextrose) to the range of subarachnoid analgesic drugs available in the United Kingdom has been welcomed (Editorial, 1983). The 0.5% glucose-free bupivacaine solution (isobaric, plain) has been the subject of intense investigation and many studies have demonstrated its efficacy (Nolte et al., 1977; Cameron et al., 1981; Ryan, Pridie and Copeland, 1983). However, controversy exists regarding the predictability of the segmental levels of analgesia achieved with the plain solution (Cameron, 1982; Nolte and Farrar, 1982; Russell, 1982; Stoneham and Moss, 1983), and some investigations suggest that hyperbaric bupivacaine provides a more predictable level of blockade (Goodison, 1982; Phelan and MacEvilly, 1984). Double-blind trials of isobaric and hyperbaric solutions of amethocaine and bupivacaine have revealed distinct differences in their behaviour when used to provide subarachnoid analgesia for non-pregnant patients. The hyperbaric solutions always spread further and have a shorter duration of action than equal volumes of the plain solutions (Wildsmith et al., 1981; Chambers et al., 1982; Phelan and MacEvilly, 1984).

Spinal analgesia with plain 0.5% bupivacaine solution provides good operating conditions for Caesarean section, but does produce occasional unexpectedly high dermatomal spread (Russell, 1982, 1983), and Stoneham and Moss (1983) have described a total spinal following the use of 3.0 ml for Caesarean section. Recent studies of subarachnoid analgesia for Caesarean section using hyperbaric bupivacaine 2.0–3.0 ml have shown that good operating conditions can be obtained (Wildeck-Lund, Lyrenas and Edstrom, 1983; Russell and Holmqvist, unpublished results), although Santos and colleagues (1984), using 1.5–2.0 ml, found surgical anaesthesia was inadequate despite apparently satisfactory levels of cutaneous analgesia. The present double-blind trial was undertaken since no previous study of spinal anaesthesia for Caesarean section has made a direct comparison between 0.5% plain bupivacaine and 0.5 % hyperbaric bupivacaine, and it is not known whether either drug possesses any clinical advantage.

PATIENTS AND METHODS

Forty patients undergoing Caesarean section under spinal anaesthesia were included. They were randomly allocated to receive either 0.5%

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glucose-free bupivacaine 2.5 ml (isobaric) or 0.5% bupivacaine in 8% glucose 2.5 ml (hyperbaric, Astra).

The investigation was performed in accordance with the Helsinki Declaration, and was approved by the Ethics and Clinical Trial Subcommittee, Hull Royal Infirmary, and the Obstetric Staff Committee, Hull Maternity Hospital.

One patient in the hyperbaric group was excluded from the analysis as a result of a deviation from the design of the study (she had the wedge placed under the left hip). The grouped data for the remaining 39 patients are shown in table I. Both groups were comparable. Five patients in the isobaric group and two in the hyperbaric group were obese before pregnancy (80 kg or more). One patient in each group had untreated essential hypertension and neither received prophylactic i.m. ephedrine. One patient in each group required an emergency Caesarean section for prolapsed cord.

Ephedrine 20 mg i.m. was administered 22–61 min before operation to minimize hypotension, while sodium citrate 0.3 mol litre^{-1} (20–30 ml by mouth) was used as an antacid. All patients were given a preload of Hartmann's solution 1000 ml i.v. immediately before the subarachnoid injection.

While the patient lay in the right lateral position, lumbar puncture was performed, with a 25-gauge needle, using a standard midline approach, at either the L2–3 or the L3–4 space. Once a free flow of cerebrospinal fluid was obtained, 2.5 ml of the chosen solution was injected at 4–5 s ml^{-1} without barbotage. Immediately after the injection the patients were turned supine and a wedge was placed under the right hip.

TABLE I. *Patient characteristics*

	Age (yr)	Height (cm)	Weight at booking (kg)	Weight at partus (kg)
Isobaric				
Mean	29	161	68	79
SD	4.9	6.9	15.2	14.8
SEM	1.1	1.6	3.4	3.3
n	20	20	20	20
Hyperbaric				
Mean	28	162	66	78
SD	4.3	6.3	15.3	13.9
SEM	1.0	1.5	3.5	3.2
n	19	19	19	19

The patients breathed oxygen 6 litre min^{-1} from a Hudson mask until the baby was delivered. After delivery of the baby, supplementary analgesia with nitrous oxide 6 litre min^{-1} in oxygen 2 litre min^{-1} and trichloroethylene, as required, was provided through this mask. Verbal contact with the patients was maintained at all times while they breathed this mixture.

Analgesia (defined as the loss of sharp sensation to pin prick with the blunt end of a Sherwood B400 27-gauge short needle) was assessed at 2, 5, 10, 15, 20 and 30 min and thereafter at 15–30 min intervals.

Motor blockade of the lower limbs was assessed on the Bromage scale: 0 = no paralysis (full flexion of the knees and feet); 1 = inability to raise extended leg (just able to move knees); 2 = inability to flex knees (able to move feet only); 3 = inability to flex ankle joint (unable to move the knees or feet).

Maternal heart rate and arterial pressure were monitored before and during anaesthesia. Hypotension, defined as a systolic arterial pressure of less than 100 mm Hg irrespective of the baseline pre-induction arterial pressure, or a decrease in systolic arterial pressure of more than 30% of the baseline value, was treated by increasing the rate of the infusion and the administration of 6-mg increments of ephedrine i.v. No i.v. ephedrine was given until hypotension occurred.

The Wilcoxon rank sum test and non-parametric confidence levels of the median were used for non-parametric tests of significance, while the t and χ^2 tests were used to compare cardiovascular changes and duration of anaesthetic effects. The results are expressed, where appropriate, as the mean ± SEM, or the median followed by the range.

RESULTS

The speed of onset of analgesia is shown in figure 1. By 5 min sensory analgesia extended to T3 (median; range C7–T10) for the hyperbaric solution and to T4 (median; range C3–T10) for the plain solution. In only four patients was the level below T8 at this time—two in each group. The maximum cephalad spread was T1 (median; range C1–T4) for the hyperbaric solution and T2 (median; range C1–T4) for the glucose-free solution. The median times to T4 were 5.5 min (range 2–15 min) for the plain solution and 4.4 min (range 2–15 min) for the hyperbaric drug,

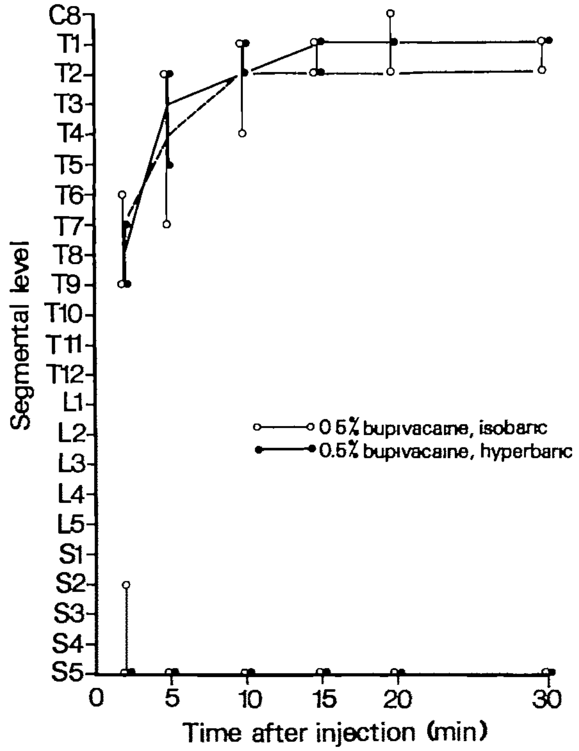

FIG. 1. Onset of analgesia (median values). $n = 20$, lower/upper bounds at 95.6% confidence level (isobaric); $n = 19$, lower/upper bounds at 93.6% confidence level (hyperbaric).

while the median time to achieve maximum spread was 15 min for each group (range 5–45 min, plain and 5–20 min, hyperbaric). High cervical levels (C1, C2) were obtained in six patients (four plain and two hyperbaric) while 11 patients overall had a cervical analgesic level measured at some time (six plain and five hyperbaric). There were no significant differences between the two solutions with respect to their speed of onset, overall extent of analgesia or number of patients attaining cervical levels of analgesia.

The segmental spread and duration of analgesia are shown in figures 2 and 3 respectively. There were fairly rapid decreases in analgesic levels, with no difference in the duration of analgesia between the groups. Surgical analgesia was satisfactory in all but one patient in the plain group—who required supplementary analgesia for a few minutes from delivery until the parietal peritoneum was closed (cutaneous analgesia during this time was T4). At 3.5 h only seven patients still had analgesia extending above the lumbar segments (five isobaric and two hyperbaric).

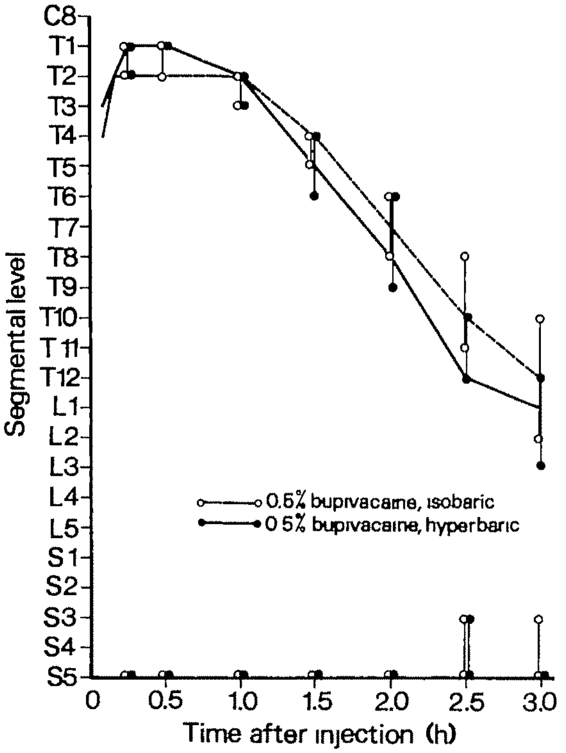

FIG. 2. Segmental spread of analgesia (median value). Lower/upper bounds at 95.6% confidence level until 2.5 h ($n = 20$) and 90.4% at 3.0 h ($n = 18$) (isobaric); lower/upper bounds at 93.6% confidence level until 2.5 h ($n = 19$) and 95.1% at 3.0 h ($n = 17$) (hyperbaric).

All patients developed complete motor blockade of the legs and this was obtained in both groups in a median time of 6 min (ranges 2–10 min isobaric and 2–6 min hyperbaric). The onset and duration of the three degrees of motor blockade are shown in table II. Motor blockade lasted significantly longer in the isobaric group ($P < 0.05$). In the left leg all three degrees of motor blockade lasted longer in the plain group, whereas only degree I lasted longer in the right leg. The longest median durations for any degree of motor blockade (degree I) were 178 min (range 118–268 min) in the plain group and 148 min (range 88–208 min) in the hyperbaric group ($P < 0.05$). Only 10 patients had any degree of motor blockade lasting for longer than 3 h (eight plain and two hyperbaric) (χ^2: $P < 0.05$).

The mean maximal decreases in systolic arterial pressure were 14±3.3% in the hyperbaric group and 3±5.4% in the isobaric group, recorded at 5 min after injection (table III). This difference

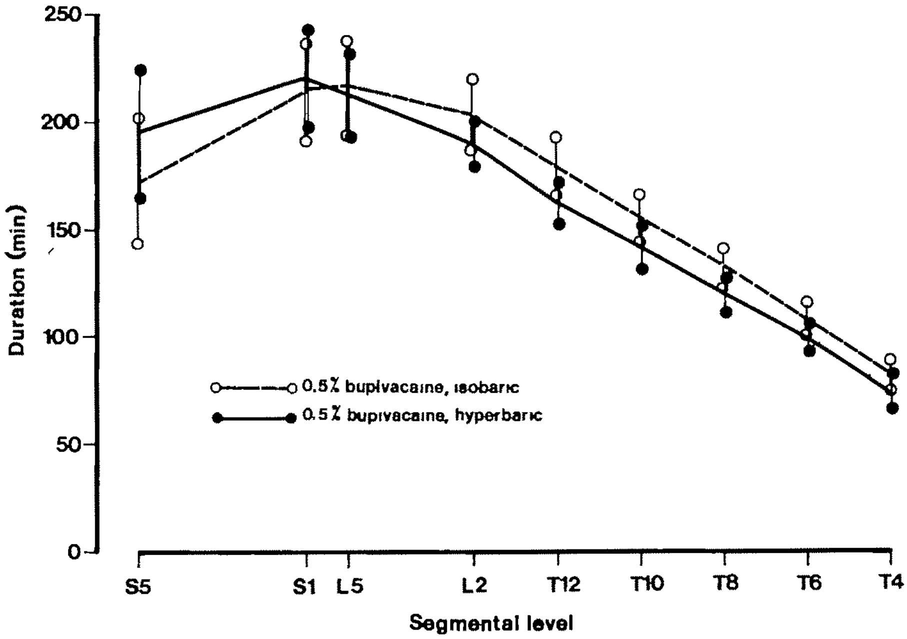

FIG. 3. Duration of analgesia at different segmental levels, mean, upper/lower bounds at 90% confidence level.

TABLE II. *Onset time (min) and duration (min) for the three degrees of motor blockade (see text) of the lower limbs, left side (median values, lower/upper quartiles). Details of motor block were not recorded for one patient (isobaric)*

Degree of blockade:	Onset time (min)			Duration (min)		
	1	2	3	1	2	3
Hyperbaric						
n	19	19	19	19	19	19
Lower quartile	2	2	2	88	84	58
Median	2	2	2	148	114	114
Upper quartile	2	6	10	178	148	118
Isobaric						
n	19	19	19	19	19	19
Lower quartile	2	2	2	148	114	88
Median	2	6	6	178	140	134
Upper quartile	2	6	10	208	204	170

was not statistically significant. The dose of ephedrine required to treat hypotension when it occurred varied from 6 to 30 mg given over 2–3 min. There was no difference in the amounts of ephedrine required in the two groups. The hyperbaric solution caused a significantly greater increase in heart rate at 2 min ($P < 0.05$), taking into account the higher pre-anaesthetic control value ($P < 0.01$) of the isobaric group. Ten patients in the plain group and 13 patients in the hyperbaric group required i.v. ephedrine for the treatment of hypotension. In nine patients (four plain and five hyperbaric) the decrease in pressure was greater than 30% of the baseline value.

The various time intervals from the induction of anaesthesia until the end of surgery are shown in table IV. There were no significant differences between the groups.

Two infants in each group had an Apgar score of 8 at 1 min. One infant in each group had a score of 7 at 1 min. The mothers of these latter infants both suffered from untreated essential hypertension and neither had received prophylactic ephedrine i.m. In one case, despite the excellent

TABLE III. *Changes in systolic arterial pressure (mm Hg) over the first 30 min of anaesthesia*

	Before inj.	After injection (min)					
		2	5	10	15	20	30
Hyperbaric							
Mean	129	126	111	120	127	128	125
SD	17.3	18.7	17.7	14.3	21.8	14.3	11.8
Isobaric							
Mean	122	128	118	125	131	129	130
SD	14.6	16.0	23.0	18.7	21.6	17.8	16.8

TABLE IV. *Various time intervals from induction of anaesthesia until end of surgery. I–D = Induction to delivery; U–D = uterine incision to delivery*

	I–D interval (min)	U–D interval (s)	Duration of op. (min)
Isobaric			
Mean	23.95	88.40	34.05
SD	6.89	58.21	10.37
SEM	1.54	13.02	2.32
n	20	20	20
Hyperbaric			
Mean	22.74	95.16	30.53
SD	7.44	74.54	8.10
SEM	1.71	17.10	1.86
n	19	19	19

analgesia and abdominal muscle relaxation, there was considerable difficulty in delivering the infant, resulting in a prolonged uterine incision to delivery (U–D) interval of more than 6 min (384 s). At 5 min the Apgar score was still only 8, but there were no long-term problems. The arterial pressure in the period immediately before operation for the second patient varied between 170 and 150 mm Hg systolic and between 130 and 105 mm Hg diastolic. Following the induction of intrathecal anaesthesia, no ephedrine was used and her systolic pressure was allowed to decrease to 115 mm Hg (29% of control) just before the delivery of the infant. However, later calculation estimated the decrease in mean arterial pressure for the 2 min before delivery at 40%. This infant had a normal Apgar score at 5 min.

Nine patients (four plain and five hyperbaric) developed a post-spinal headache (23%) and were treated initially with bed rest and analgesics by mouth. Three of these subsequently required a blood patch (two plain and one hyperbaric). Thirteen patients (six isobaric and seven hyperbaric) were given metoclopramide i.v. during surgery to treat nausea, and one patient (plain) vomited.

DISCUSSION

There were no significant differences in the onset, maximum spread or duration of analgesia between the hyperbaric and the plain 0.5% bupivacaine groups. This is quite different from the behaviour of these solutions when they are used to provide subarachnoid analgesia in non-pregnant patients in whom hyperbaric bupivacaine spreads 3–5 segments further than the plain solution (Chambers, Edstrom and Scott, 1981; Phelan and MacEvilly, 1984). Similar results in non-pregnant patients were obtained with isobaric and hyperbaric amethocaine (Brown et al., 1980; Wildsmith et al., 1981). As a result of the more restricted spread and, consequently, a higher drug concentration in the CSF, the isobaric solutions always last much longer (Brown et al., 1980; Wildsmith et al., 1981; Phelan and MacEvilly, 1984). Since both bupivacaine solutions spread to an equal extent in pregnant patients, it is not unreasonable that analgesia should wear off at similar rates in both groups.

The similarity of the dermatomal spread in both groups suggests that pregnancy has a more marked effect on the spread of the plain than the hyperbaric solution when the differences between non-pregnant and pregnant levels are compared. In non-pregnant patients, plain bupivacaine 3–4 ml injected with the patient in a lateral position usually results in analgesic levels in the lower thoracic dermatomes—T9 or T10 (Chambers, Edstrom and Scott, 1981; Tattersall, 1983; Phelan and MacEvilly, 1984; Russell, 1984)—while hyperbaric bupivacaine 3.0 ml in similar patients reaches the upper thoracic dermatomes—T4 or T5 (Chambers, Edstrom and Scott, 1981; Chambers et al., 1982; Phelan and MacEvilly, 1984). In the present study, the slightly smaller volumes used only resulted in analgesia extending by 3 or 4 more segments, to T1, in the hyperbaric group but by 7 or 8 segments, to T2, in the plain group (that is, pregnancy enhances the spread of plain bupivacaine more than the spread of hyperbaric bupivacaine).

The reasons for this differential effect are speculative, but it could be explained by the properties of the two drugs in relation to gravity and the mass movement of CSF as a result of the postural changes described in previous publications (Russell, 1983, 1984). Gravity will tend to keep the hyperbaric solution near the lowest point of the thoracic curve (T4/T5 in the supine position) and to resist attempts to move it any further in a cranial direction. This tendency could be further assisted by the viscosity of the hyperbaric solution, preventing it mixing with the CSF (Scott and Sinclair, 1982), thus allowing CSF to sweep past as it is displaced by engorging extradural veins in the thoraco–lumbar area. The plain solution, however, mixing freely with CSF, has neither gravitational nor viscous effects to constrain its movement within the displaced CSF. The contribution made towards the spread of analgesia by the mass movement of CSF and whether the effects of gravity are in the same direction or not will determine if hyperbaric solutions spread more than isobaric solutions. The traditional explanation that isobaric solutions are unaffected by posture, while hyperbaric solutions merely spread down into the hollow of the thoracic curve under the influence of gravity (Barker, 1907; Brown et al., 1980), requires reappraisal in pregnant patients and, probably, in non-pregnant patients also (Russell, 1983, 1984).

Only one patient in this study required supplementary analgesia (isobaric group). This was given for a short time during the closure of the parietal peritoneum. This is in sharp contrast to the findings of Santos and colleagues (1984): 21 of 22 pregnant patients given hyperbaric bupivacaine 1.5–2.0 ml needed additional analgesia. However, the slightly larger dose used in the present study resulted in analgesia extending up to C1/C2 in six patients, with consequent total body analgesia except for the face. Three of these women weighed 100 kg or more; one weighed 82 kg and was only 155 cm tall; the fifth was only 151 cm in height (less than 5 feet). There was no identifiable reason why there should have been such a high level of analgesia in the sixth patient. These high analgesic levels caused neither ventilatory difficulty nor any other clinical problems. This is quite different from the situation following 5% heavy lignocaine 1.3–1.5 ml, where four of 30 patients had high levels resulting in considerable weakness of the arms, difficulty in breathing and an inability to swallow saliva (Bembridge, MacDonald and Lyons, 1986). Crawford (personal communication) has also described a total spinal following heavy lignocaine 1.5 ml for a forceps delivery. These findings suggest that 0.5% bupivacaine solutions can produce a wide area of differential blockade, with analgesia extending considerably higher than any motor blockade. Problems have occurred with slightly larger doses of plain bupivacaine when used to provide spinal anaesthesia for Caesarean section. Russell (1985) has described a total spinal following 0.75% plain bupivacaine 2.0 ml (15 mg), while Stoneham and Moss (1983) have reported a similar episode after 0.5% plain bupivacaine 3.0 ml (15 mg). On the other hand, Goodison (1982) used large volumes (5 ml) of a 0.4% hyperbaric bupivacaine solution (20 mg) for Caesarean section with no untoward effects. Whether this suggests an increased safety margin with the hyperbaric solution is unknown. Theoretically, as discussed above, it could, but the evidence from the present limited study does not give any real guidance on this aspect.

Although, in general, the hyperbaric solution caused the greater changes in cardiovascular indices, only the increase in heart rate at 2 min was statistically significant ($P < 0.05$). This was also reflected in the greater use of i.v. ephedrine in the hyperbaric group, in which 13 patients required treatment for hypotension as compared with 10 in the plain group. The use of prophylactic i.m. ephedrine seems to have little to recommend it. The dose used in this study was not very effective, while larger more effective doses cause reactive hypertension (Gutsche, 1976). Other disadvantages of the i.m. route are unpredictable absorption and difficulty in estimating the time to peak effect, not to mention the problems of operation schedules in a busy unit. Ephedrine is best given i.v. prophylactically to avoid any clinically significant decrease in arterial pressure (Datta et al., 1982; Kang, Abouleish and Caritis, 1982). Waiting until a predetermined level of hypotension occurs before initiating treatment cannot be recommended, even if the hypotension is of short duration and has little effect on the infant (Kang, Abouleish and Caritis, 1982) since rapid changes in arterial pressure are often associated with nausea and vomiting (Datta et al., 1982; Kang, Abouleish and Caritis, 1982).

One infant in each group had an unacceptably low Apgar score (7) at 1 min and in both the mothers had untreated essential hypertension. The prolonged U–D interval in one of these (more than 6 min) could account for the low score on its own, but it should be noted that there was no similar delay in the other low score infant. The systolic arterial pressure of the mother of the second infant with a low Apgar score did not decrease below 115 mm Hg (29% of control), but the decrease in mean arterial pressure at this time was later calculated at 40%. Neither of these mothers had received prophylactic ephedrine i.m. It may be that in patients with hypertension the arterial pressure should be kept as close to the patient's "normal" value as possible to minimize possible decreases in placental perfusion. This could perhaps be achieved by the judicious use of i.v. ephedrine.

With nine patients (23%) developing a post-spinal headache, this was the biggest problem, but there was no significant difference between the groups. Three patients subsequently required a blood patch. Although Brownridge (1984) did not find any consistent pattern in relation to spinal headache in pregnant patients, a recent study of non-pregnant patients demonstrated that the incidence of post-spinal headache could be reduced from 16% to 0.24% by turning the bevel of the spinal needle parallel to the longitudinal fibres of the dura (Mihic, 1985). The present authors have since modified their technique and, in the most recent 50 patients undergoing spinal anaesthesia for Caesarean section, the needle bevel was parallel to the dural fibres. None developed a headache, although past experience would predict that 20–25% would have done so.

In conclusion, the results of this study confirm that when hyperbaric or plain 0.5% bupivacaine 2.5 ml is used as described, both provide rapid, effective anaesthesia for Caesarean section. There does not appear to be any clinically relevant difference in the behaviour of the two drugs.

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DOUBLE-BLIND COMPARISON OF THE EFFICACY OF EXTRADURAL DIAMORPHINE, EXTRADURAL PHENOPERIDINE AND I.M. DIAMORPHINE FOLLOWING CAESAREAN SECTION

D. J. MACRAE, S. MUNISHANKRAPPA, L. M. BURROW, M. K. MILNE AND I. S. GRANT

SUMMARY

A randomized, double-blind study of the efficacy, duration of action and side effects of three analgesic regimens following Caesarean section is described. Patients received i.m. diamorphine 5 mg, extradural phenoperidine 2 mg or extradural diamorphine 5 mg. Analgesia was of rapid onset in all groups, as judged by reductions in linear analogue pain scores and rank pain scores. Time to next analgesia was significantly greater after extradural phenoperidine (5.96 h) and extradural diamorphine (8.39 h) than after i.m. diamorphine (3.40 h) ($P < 0.001$). Itching was reported on direct questioning by 50% of patients in the extradural groups. No serious side effects were reported. Factors affecting the disposition of extradurally administered diamorphine are discussed.

Since the first report of the extradural administration of opioids in man (Behar et al., 1979) the technique has been used to provide analgesia in many situations. Early reports of analgesia of long duration without major side effects have been followed by more cautious claims, with reports of side effects such as late ventilatory depression, urinary retention, itching and vomiting (Bullingham, McQuay and Moore, 1982; Morgan, 1982).

Extradural morphine has been investigated extensively in studies of postoperative analgesia following Caesarean section. Controlled studies have been small, and varied in their conclusions on efficacy (Youngstrom et al., 1982; Chambers, Mowbray and Wilson, 1983; Cohen and Woods, 1983). Ventilatory depression has been noted, especially with larger doses (8–10 mg) (Carmichael, Rolbin and Hew, 1982).

There have also been reports of the use of extradural fentanyl and diamorphine (Houlton and Reynolds, 1981), pethidine (Brownridge, 1983) and methadone (Beeby et al., 1984) to provide postoperative analgesia following Caesarean section. All claim satisfactory analgesia without serious side effects. Extradural phenoperidine 1–2 mg has been administered to more than 1000 patients in Ninewells Hospital, with apparently satisfactory analgesia and no serious side effects.

Diamorphine, being highly lipid soluble, may be safer than the more hydrophilic morphine in its spinal application, since it will be cleared more rapidly from the cerebrospinal fluid (Moore et al., 1984; Phillips et al., 1984). Its subsequent metabolism in neural tissue to monoacetyl morphine and morphine (Way et al., 1960) may explain the clinical observation that its duration of action after extradural administration is similar to that of morphine (Barron and Strong, 1981). However, studies by Jacobson and Malins failed to establish clearly its efficacy in comparison with i.m. administration (Jacobson et al., 1983; Malins et al., 1984).

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TABLE I. *Analgesic regimens. †Diamorphine hydrochloride monohydrate 5 mg (Diamorphine injection B.P., Evans Medical Limited). *Phenoperidine hydrochloride injection 2 mg (Operidine, Janssen Pharmaceutical Limited)*

Analgesic regimen	Extradural injection	I.m. injection
Diamorphine i.m.	0.9% Sodium chloride 10 ml	Diamorphine 5 mg† in 0.9% sodium chloride 1 ml
Extradural phenoperidine	Phenoperidine 2 mg* in 0.9% sodium chloride 10 ml	0.9% Sodium chloride 1 ml
Extradural diamorphine	Diamorphine 5 mg† in 0.9% sodium chloride 10 ml	0.9% Sodium chloride 1 ml

This study was designed to establish the intensity and duration of analgesia, and the frequency of side effects, attributable to the use of extradural diamorphine, and to compare the findings with those associated with the extradural administration of phenoperidine and the administration of diamorphine i.m.

PATIENTS AND METHODS

Sixty patients (ASA grades I or II) who had undergone Caesarean section under lumbar extradural blockade, were included in the study. Informed consent and the approval of the Hospital Ethical Committee were obtained.

Lumbar extradural blockade was established using bupivacaine either 0.75% (14 patients) or 0.5% (46 patients), the change being necessitated when the manufacturer altered the data sheet to exclude use of the 0.75% preparation in obstetric analgesia. No opiate analgesia was given either during labour or in association with the Caesarean section. Twenty-one patients were given a small dose of midazolam (2.5–5 mg) as a sedative following the delivery of the infant.

Following the operation the patients were asked to request analgesia if they felt uncomfortable. At this point they were visited by an anaesthetist observer (S.M. or D.J.M.) and an initial assessment was made. Heart rate, ventilation rate and arterial pressure were recorded, and patients were asked to complete a 10-cm horizontal linear analogue pain score (LAPS) (Revill et al., 1976), a rank pain score (RPS) (none = 0; mild = 1; moderate = 2; severe = 3) and a rank sedation score (RSS) (sleeping = 0; very drowsy = 1 drowsy = 2; wide awake = 3). Presence of nausea, vomiting, itching or other complaints was noted.

Patients were then randomly allocated to one of the three analgesic regimens: diamorphine 5 mg i.m.; extradural phenoperidine 2 mg or extradural diamorphine 5 mg. All received an extradural injection via their *in situ* catheter and bacterial filter, and an i.m. injection (table I). The randomizations, which were carried out using a table of random numbers, took account of the emergency or elective nature of the Caesarean section. The 10-ml extradural injection and 1-ml i.m. injection were drawn up by another anaesthetist, and both observer and patient remained unaware of the drug given, or its route of administration.

Further assessments were performed by the same observer at 15 and 30 min, and at 1, 2, 4, 8, 12 and 18 h after the initial administration of the analgesic. Patients were free to request additional analgesia, and on doing so they were withdrawn from the study and the time recorded as time to next analgesia (TNA).

Results were subjected to statistical analysis by Student's *t* test, paired or unpaired, or Chi squared test with Yates' correction, as appropriate.

RESULTS

The mean ages and weights of patients in each group are shown in table II. There were no significant differences between the groups. The mean times to next analgesia (TNA) for each group are shown in table III. Both extradural regimens resulted in significantly longer TNA than the i.m. group ($P < 0.001$). The longer TNA

TABLE II. *Clinical data of investigated patients (mean ± SEM). No statistically significant differences exist between groups (Student's t test)*

Analgesic regimen	Age (yr)	Weight (kg)
Diamorphine i.m. ($n = 20$)	27.1 ± 1.2	70.2 ± 2.6
Extradural phenoperidine ($n = 20$)	28.1 ± 1.2	67.6 ± 2.6
Extradural diamorphine ($n = 20$)	28.8 ± 1.4	72.6 ± 2.4

TABLE III. *Time to next analgesia. Statistical significance calculated using Student's t test*

Analgesic regimen	Time to next analgesia (h) (mean ± SEM)	*P*	
Diamorphine i.m.	3.40 ± 0.47	< 0.001	< 0.001
Extradural phenoperidine	5.96 ± 0.43		
Extradural diamorphine	8.39 ± 1.15	= 0.05	

of the extradural diamorphine group just achieved statistical significance ($P = 0.05$) over that of the extradural phenoperidine group.

Mean linear analogue pain scores (LAPS) are shown in table IV. Reductions in LAPS were significant ($P < 0.001$) in all groups by 15 min. Figure 1 displays the number of patients achieving an LAPS of less than 2.5 cm at the times shown. The trend of extradural diamorphine to produce a longer duration of analgesia when compared with diamorphine i.m. and, to a lesser extent, with extradural phenoperidine, is illustrated. Figure 2 displays mean rank pain scores up to 240 min. Significant differences between groups are indicated. No significant differences in LAPS or RPS existed between the extradural groups at any time.

With the onset of analgesia, a reduction in rank sedation scores occurred in all groups. Scores remained significantly reduced compared with control values ($P \leqslant 0.02$) at all points shown in figure 3. No significant differences existed between the groups except at 120 min when, despite the waning of analgesic effect, patients in the i.m. group were significantly less alert than those in the extradural phenoperidine group ($P < 0.02$).

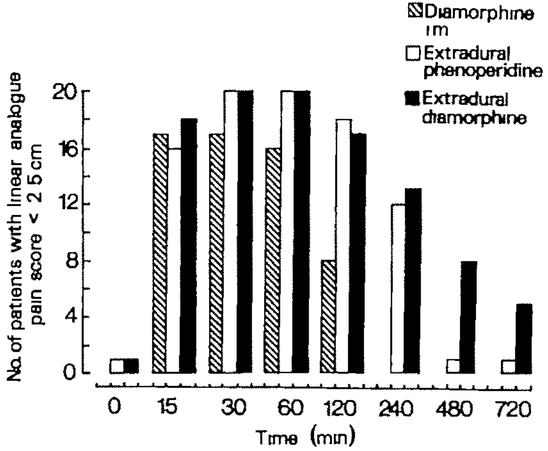

FIG. 1. Number of patients with linear analogue pain scores of less than 2.5 cm up to 720 min.

Adverse effects occurring in the study are shown in table V. No significant changes in heart rate or arterial pressure were detected. A modest decrease in ventilation rate occurred in each group with the onset of analgesia. The mean (± SEM) control ventilation rate (b.p.m.) for all patients was 19.1 ± 1.05, whilst the corresponding figures for

TABLE IV. *Linear analogue pain scores (mean ± SEM). Numbers of patients remaining in each group at specified times are indicated in parentheses. Statistical significance of reductions in score from zero values (paired* t *test) are indicated.* **P < 0.01; ***P < 0.001

	Linear analogue pain score (cm)		
Time (min)	Diamorphine (i.m.)	Extradural phenoperidine	Extradural diamorphine
0	5.5 ± 0.39 (n = 20)	5.6 ± 0.36 (n = 20)	5.2 ± 0.43 (n = 20)
15	1.0 ± 0.39*** (n = 20)	0.9 ± 0.35*** (n = 20)	1.1 ± 0.27*** (n = 20)
30	1.0 ± 0.32*** (n = 20)	0.3 ± 0.16*** (n = 20)	0.3 ± 0.13*** (n = 20)
60	1.3 ± 0.43*** (n = 20)	0.1 ± 0.57*** (n = 20)	0.3 ± 0.12*** (n = 20)
120	3.1 ± 0.71** (n = 17)	0.4 ± 0.27*** (n = 20)	0.9 ± 0.38*** (n = 19)
240	4.5 ± 1.19 (n = 4)	1.8 ± 0.59*** (n = 18)	0.8 ± 0.32*** (n = 15)
480	3.6 (n = 2)	2.3 (n = 2)	0.7 ± 0.37*** (n = 9)
720		0 (n = 1)	0.6 ± 0.56*** (n = 5)

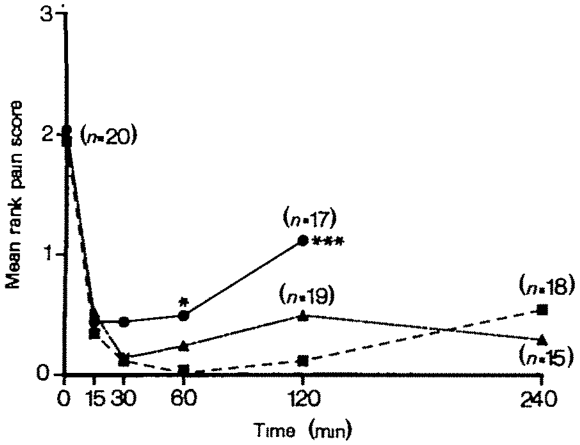

FIG. 2. Mean rank pain scores up to 240 min for diamorphine i.m. (●——●), extradural phenoperidine (■---■), and extradural diamorphine (▲——▲) groups. Significant differences between groups as indicated (Chi squared test): *i.m. *v.* extradural phenoperidine ($P < 0.05$); ***i.m. *v.* extradural phenoperidine ($P < 0.001$). Reductions in RPS compared with zero values significant at a level $P < 0.01$ or greater at all points charted.

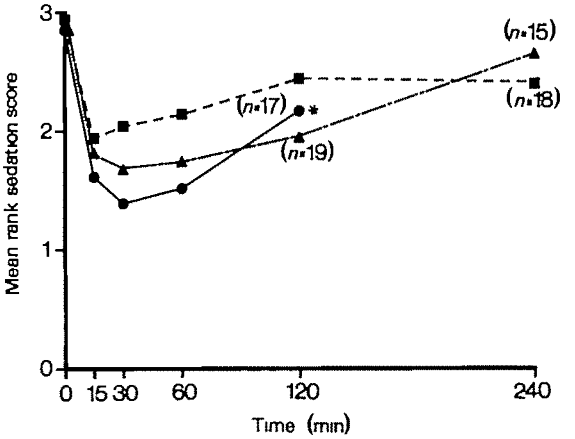

FIG. 3. Mean rank sedation scores up to 240 min after diamorphine i.m. (●——●), extradural phenoperidine (■---■), and extradural diamorphine ▲——▲ are shown. No significant differences exist between groups except *i.m. *v.* extradural phenoperidine ($P < 0.02$) (Chi squared test). Sleeping = 0; very drowsy = 1; drowsy = 2; wide awake = 3.

30 min were 17.3±0.92. There were no statistically significant differences between groups. Only three patients were noted to have ventilation rates of less than 12 b.p.m., two from the i.m. group and one from the extradural phenoperidine group. These rates were evident 15 min following injection. No rate of less than 12 b.p.m. was recorded after 120 min post-injection.

TABLE V. *Adverse effects (numbers of patients). Statistical significance by Chi squared test* (P < *0.001*)*: †i.m. diamorphine* v. *extradural phenoperidine; ‡i.m. diamorphine* v. *extradural diamorphine*

Adverse effect	Diamorphine i.m.	Extradural phenoperidine	Extradural diamorphine
Nausea	1	1	3
Vomiting	0	0	2
Itching	0	9†	11‡
Sweating	4	0	2
Ventilation rate < 10 b.p.m.	0	0	0
Heart rate < 60 beat min^{-1}	0	0	0
Systolic arterial pressure decrease > 20%	0	0	0

Nausea was reported by five patients and two of these also vomited. There were no statistically significant differences between groups.

Itching achieved a combined incidence of 50% in the extradural groups, being sought by direct questioning. No patient in the i.m. group reported itching. Only one patient was sufficiently distressed by itching to require treatment. In others the effect was minimal and often of short duration, and was most commonly noted between the 30- and 120-min intervals.

Sweating was reported by six patients. None of these patients was among those in whom ventilation rates of less than 12 b.p.m. were recorded. No other adverse effects were reported.

DISCUSSION

We have demonstrated that extradural diamorphine produces more prolonged and intense analgesia and, possibly, less sedation than i.m. diamorphine in the same dose. Extradural phenoperidine had a similar, though less prolonged, effect. We found no major adverse effects with either of the drugs when administered extradurally.

Previous studies comparing i.m. and extradural diamorphine for postoperative pain relief have produced conflicting results. Jacobson and colleagues (1983), studying patients after thoracotomy or gynaecological laparotomy, found no difference in the quality of analgesia produced by i.m. or extradural diamorphine 0.1 mg kg^{-1}. However, mean durations of analgesia following i.m. administration, at 9.3 h and 6 h in the thoracotomy and gynaecological surgery groups, respectively, were surprisingly long. Although duration of analgesia following extradural administration was significantly greater, Jacobson and his colleagues (1983) concluded that it appeared to be simply "an exotic method of administering a systemic opioid".

Malins and colleagues (1984), comparing the ventilatory effects of i.m. and extradural diamorphine 5 mg after aortic aneurysm surgery found quality and duration of analgesia after i.m. diamorphine so inferior to that of extradural diamorphine that their study was curtailed after only six patients had received i.m. diamorphine.

We cannot reconcile our results following i.m. administration with those of Jacobson and colleagues (1983), but the duration of analgesia following i.m. diamorphine (TNA 3.4 ± 0.47 h) was consistent with our clinical experience with this drug. The mean duration of analgesia of the extradural diamorphine group of 8.39 h encompassed a large range from 3 to 19 h, and is similar to that described by Jacobson and colleagues (1983). This variation of analgesic effect may reflect the variable systemic uptake of diamorphine from the extradural site.

It has been shown (Moore et al., 1982) that transfer of a drug across the dura mater *in vitro* is mainly a process of diffusion, and thus depends on the concentration gradient of the drug across the dura, which would be affected by systemic absorption from the extradural space.

Phillips and colleagues (1984) found that peak plasma morphine concentrations were greater, and occurred earlier, after thoracic extradural diamorphine 2 mg than after extradural morphine 2 mg. These findings were confirmed by Watson and co-workers (1984) for lumbar extradural administration of the same drugs. These authors applied their results to the formulae described by Moore and associates (1982) on disposition of drugs placed in the extradural space, and predicted that the dural transfer of diamorphine would be only 55% of that of an equimolar dose of morphine, because of the rapid systemic absorption of diamorphine resulting from its higher lipid solubility. The systemic absorption of diamorphine may be even more rapid in pregnancy, as a result of increased extradural blood flow, and the transdural concentration gradient—which determines transfer of the drug—would be further decreased.

Phenoperidine, which is less lipid soluble than diamorphine, may have a higher fractional dural transfer because of slower systemic absorption and a higher transdural concentration gradient. Our results show a more predictable duration of action following phenoperidine (range 5–12 mean 5.96 h). Lipophilicity does confer the important advantage of rapid CSF clearance, which is thought to be of benefit in reducing the frequency of late ventilatory depression (Moore et al., 1984). In addition, the metabolism of diamorphine to the more hydrophilic monoacetyl morphine and morphine in neural tissue (Way et al., 1960) could confer a further advantage, namely, a prolonged duration of action compared with other lipophilic opioids, similar to that of morphine.

If the systemic absorption of diamorphine can be slowed in the early phase, allowing a greater fractional transfer into CSF, then a more predictable duration of analgesia may be achieved. The addition of adrenaline to the extradural injectate may be effective in this respect, although there are reported hazards associated with its use in the extradural space.

We found no evidence of ventilatory depression, early or late, as judged by ventilation rate. Previous studies (Cooper et al., 1982; Malins et al., 1984) have also failed to detect any clinically significant ventilatory depression after extradural diamorphine. The incidence of itching noted in the extradural groups was similar to that reported in other studies of extradural opioids (pethidine 50 mg (Brownridge, 1983); morphine (Cohen and Woods (1983)). All our patients had urinary catheters in place, and no attempt could be made to define the frequency of urinary retention, which has been previously reported during use of extradural opioids (Cousins and Mather, 1984).

In conclusion, the extradural administration of diamorphine or of phenoperidine provided analgesia of greater intensity and duration than i.m. diamorphine, following Caesarean section. Phenoperidine provided more limited duration of analgesia than diamorphine and had no particular advantages. Diamorphine would appear to be effective, free of serious adverse effects, and may be the drug of choice for extradural administration. It remains to be seen whether the addition of adrenaline would increase the predictability of the duration of analgesia.

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FRESH GAS FLOW REQUIREMENTS USING THE ADE ANAESTHETIC SYSTEM DURING LATE PREGNANCY

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SUMMARY

Thirty-two pregnant patients at term undergoing elective Caesarean section were ventilated with a non-co-axial ADE anaesthetic system (E mode) supplied with fresh gas flows (FGF) of either 70 or 100 ml kg^{-1} min^{-1}, on a random basis. Ventilation with an FGF of 70 ml kg^{-1} min^{-1} produced mean Pa_{CO_2} *and* PE'_{CO_2} *values of 6.48 ± 1.15 kPa and 6.41 ± 0.76 kPa, respectively. Patients were thus hypercapnic, which contrasts with the normocapnia achieved using an FGF of 100 ml kg^{-1} min^{-1} via the ADE system (E mode)* (Pa_{CO_2} *5.07 ± 0.7 kPa;* PE'_{CO_2} *4.83 ± 0.46 kPa) (mean values ± SD). The latter FGF is therefore recommended for the pregnant patient at term when using a Mapleson E system such as the Humphrey ADE apparatus.*

Humphrey (1983) described a new simple, "universal" anaesthetic system which had the capability of changing from Mapleson A to D or E configurations at the flick of two levers. He showed that, in the E configuration, the breathing system functioned as a Bain system (Bain and Spoerel, 1972) when used for intermittent positive pressure ventilation (IPPV).

The production of carbon dioxide is increased by 35% in pregnant women at term (Templeton and Kelman, 1976), and the partial pressure of arterial carbon dioxide (Pa_{CO_2}) can be predicted ($Pa_{CO_2} = k \times \dot{V}CO_2/\dot{V}FGF$ (where k is a constant, $\dot{V}CO_2$ equals the volume of carbon dioxide production and $\dot{V}FGF$ is the fresh gas flow)) when using Mapleson E systems during IPPV (Baraka, 1969; Spoerel, 1980). Therefore, in pregnant women at term, a 35% increase in fresh gas flow should be necessary to maintain Pa_{CO_2} at pre-anaesthetic values when using such apparatus.

We have compared the maternal Pa_{CO_2} and PE'_{CO_2} values attained with FGF of 70 and 100 ml kg^{-1} min^{-1} administered via the ADE anaesthetic system set in the E mode in 32 women requiring elective Caesarean section.

PATIENTS AND METHODS

Thirty-two healthy women (aged 16–40 yr; 38–42 weeks gestation) scheduled for elective Caesarean section, were randomly allocated to one of two groups to receive FGF of either 70 or 100 ml kg^{-1} min^{-1}. Patients with evidence of cardiopulmonary disease, hypertension or gross obesity (> 110 kg) were excluded. Informed patient consent and institutional approval were obtained.

The patients were premedicated with 30 ml of sodium citrate 0.3 mol litre^{-1} given orally 1–1.5 h before operation. They were placed on the operating table in the left lateral tilt position. An i.v. infusion of 1 litre of lactated balanced salt solution was commenced.

The anaesthetic technique was standardized and comprised domperidone 10 mg i.v.; pre-oxygenation for 5–10 min with the ADE system in the A configuration; and the rapid sequence induction of anaesthesia (thiopentone 3.5 mg kg^{-1} and suxamethonium 100 mg) while cricoid pressure was applied. After intubation of the trachea, and confirmation of the correct placement of the tracheal tube (by auscultation), the ADE system was changed to the E configuration and mechan-

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ical ventilation instituted (Penlon 200 ventilator: inspiratory time 1.5 s; expiratory time 3.0 s). Tidal volumes were set at 10 ml kg^{-1} and verified using a Wright's respirometer.

A self-calibrated Hewlett–Packard capnometer with nitrous oxide compensation, was connected between the tracheal tube and the catheter mount. Nitrous oxide and oxygen in a 1 :1 ratio with 0.5% halothane were administered at flow rates of either 70 or 100 ml kg^{-1} min^{-1} from vertically mounted, freely rotating flow meters.

Neuromuscular blockade was maintained with an initial dose of alcuronium 12.5 mg and increments of 2.5 mg, when necessary. At delivery, syntocinon 5 units was given i.v. and 15 units added to the i.v. infusion. Papaveretum 15–20 mg was administered i.v., the halothane discontinued and the ratio of nitrous oxide to oxygen was changed to 2 :1 without alteration in the flow rates.

Heart rate was recorded continuously (ECG), and arterial pressure measured before induction and then every 5 min thereafter (automated oscillometer (Sentry)). End-tidal carbon dioxide ($P\text{E}'_{\text{CO}_2}$) was recorded immediately after intubation, and every 5 min thereafter.

Arterial blood was sampled at 10–15 min after the induction of anaesthesia and $P\text{E}'_{\text{CO}_2}$ noted simultaneously. Blood samples were stored on ice while being transferred for analysis (Radiometer ABL2 automated blood-gas analyser).

The study was terminated once the neuromuscular blockade had been antagonized. Results were subjected to Student's *t* test.

RESULTS

Two patients were excluded from the study since they became hypotensive—with accompanying decreases in $P\text{E}'_{\text{CO}_2}$.

Two patients in the 70-ml group were changed to higher flow rates when a high $P\text{E}'_{\text{CO}_2}$ was associated with clinical signs of hypercarbia. These signs abated as the $P\text{E}'_{\text{CO}_2}$ decreased. The results of these two patients are included in the study, but the end point was taken as the time at which the gas flows were increased.

Of the 30 patients whose results are included, the two groups were similar in weight. Mean weight (SD) in the 70-ml group was 74.4 (13.4) kg, and 80.8 (15.7) kg in the 100-ml group. No statistical difference existed between the two groups in respect of initial $P\text{E}'_{\text{CO}_2}$ or arterial to end-tidal carbon dioxide partial pressure difference ($P\text{a}_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}$).

TABLE I. *Partial pressure (kPa) of arterial carbon dioxide minus end-tidal carbon dioxide*

	Fresh gas flow	
	100 ml kg^{-1} min^{-1}	70 ml kg^{-1} min^{-1}
Mean	0.24	0.05
Standard deviation	0.67	0.94
Minimum	−0.53	−1.24
Maximum	1.97	2.13
Range	2.5	3.37

$P\text{a}_{\text{CO}_2}$ did not correlate well with $P\text{E}'_{\text{CO}_2}$, the two groups having almost identical *r* values, but failing to reach statistical significance. ($P\text{a}_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}$) was extremely variable with negative and positive values (table I).

Following the methods of Whitesell and colleagues (1981), we used ($P\text{a}_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}$) to predict the $P\text{a}_{\text{CO}_2}$. Similarly, we used the ratio of $P\text{a}_{\text{CO}_2}$ to $P\text{E}'_{\text{CO}_2}$ in line with the findings of Perrin and co-workers (1983) (table II). In the 70-ml group, the final $P\text{E}'_{\text{CO}_2}$ was higher than the initial value in all but one patient. The mean (SD) increase in $P\text{E}'_{\text{CO}_2}$ was 1.14(0.73) kPa. In 80% of these patients, the $P\text{E}'_{\text{CO}_2}$ was still increasing at the end of the study. In contrast, in the 100-ml group, only 33% of patients had a final $P\text{E}'_{\text{CO}_2}$ which was higher than the initial measurement and then only minimally, so the mean (SD) decrease in $P\text{E}'_{\text{CO}_2}$ was 0.16(0.38) kPa ($P < 0.001$).

In the 70-ml group there was a significant ($P < 0.05$) negative correlation between the patient's weight and both the final $P\text{E}'_{\text{CO}_2}$, and the increase from initial to final $P\text{E}'_{\text{CO}_2}$ values. Such a correlation did not exist in the other group.

DISCUSSION

The Bain circuit is a lightweight anaesthetic breathing system of Mapleson D configuration originally designed for use during head and neck surgery (Bain and Spoerel, 1972). When used for IPPV with the ventilator attached to the bag mount, it becomes a Mapleson E system. When used in this way, the system functions as a partial rebreathing system (Bain and Spoerel, 1973; Spoerel, 1980) where $P\text{a}_{\text{CO}_2}$ varies predictably with the FGF supplied to the system, provided the minute ventilation ($\dot{V}$) is greater than the $\dot{V}\text{FGF}$ (Bain and Spoerel, 1972; Spoerel, 1980). Further-

TABLE II. *End-tidal carbon dioxide* (PE'_{CO_2} *and calculated arterial carbon dioxide* (Pa_{CO_2}) *values (mean and SD).* †$P < 0.02$; **$P < 0.01$; ***$P < 0.001$

	Fresh gas flows (ml kg^{-1} min^{-1})					
	PE'_{CO_2} (kPa)		Pa_{CO_2} (kPa)		Pa_{CO_2} (kPa)	
	70	100	70	100	70	100
Method of calculation			Whitesell et al. (1981)		Perrin et al. (1983)	
Initial	5.27	4.99	5.32	5.24	5.32	5.24
	(0.39)	(0.38)	(0.94)	(0.71)	(0.83)	(0.71)
High	6.49	5.16***	6.54	5.40**	6.55	5.40**
	(0.76)	(0.44)	(1.07)	(0.73)	(1.13)	(0.74)
Low	5.23	4.69***	5.28	4.94	5.29	4.91
	(0.40)	(0.40)	(0.94)	(0.75)	(0.84)	(0.72)
Mean	5.98	4.94***	6.03	5.19†	6.03	5.18**
	(0.60)	(0.42)	(0.94)	(0.73)	(0.93)	(0.73)
Final	6.41	4.83***	6.46	5.08***	6.48	5.07***
	(0.76)	(0.46)	(1.09)	(0.74)	(1.15)	(0.74)

more, at an FGF of 70 ml kg^{-1} min^{-1}, normocarbia is achieved (Bain and Spoerel, 1973; Henville and Adams, 1976).

The concentration of alveolar carbon dioxide is equal to $\dot{V}CO_2/\dot{V}FGF$, providing there is complete mixing of fresh gas with alveolar gas (Baraka, 1969; Bain and Spoerel, 1973, 1975; Spoerel, 1980). Therefore, it can be predicted that, when carbon dioxide production is increased, $\dot{V}FGF$ should be increased proportionly to maintain normocarbia.

Pregnancy is a condition in which the production of carbon dioxide is increased. Templeton and Kelman (1976) showed that $\dot{V}CO_2$ increased by 35% in pregnant women at term. Studies of women in labour have shown increases in $\dot{V}CO_2$ of up to 75% above values in non-pregnant individuals (Fisher and Prys-Roberts, 1968). Thus we decided to confine our study to women at term who were not in labour.

Although $\dot{V}CO_2$ is increased, awake pregnant women hyperventilate to a greater extent than is necessary to maintain Pa_{CO_2} at normal values. Minute volume is increased by 42% above non-pregnant values (Cugell et al., 1953) and, usually, results in a compensated respiratory alkalosis (Stenger et al., 1964; Blechner et al., 1968; Templeton and Kelman, 1976; Chappell, 1978). This hyperventilation is attributed to the action of progesterone (Boutourline-Young and Boutourline-Young, 1956).

The increase in FGF to 100 ml kg^{-1} min^{-1} was a 43% increase over that normally recommended to maintain normocarbia when the Bain system is used during IPPV. This increase in FGF matches the increase in ventilation at term, so it might be predicted that the mild hypocarbia of pregnancy would be maintained during IPPV by this increase in FGF.

Humphrey (1983) described a new anaesthetic breathing system which could be changed readily from a Mapleson A to a Mapleson D or E configuration. He showed that, during IPPV in the E configuration, the system behaved as a Bain breathing system and maintained normocarbia with an FGF of 70 ml kg^{-1} min^{-1}. The use of this breathing system in pregnant women had not been investigated.

The measurement of PE'_{CO_2} by capnography is a recognized technique for monitoring Pa_{CO_2} indirectly during anaesthesia (Nunn and Hill, 1960; Takki, Aromaa and Kauste, 1972). Different values for mean ($Pa_{CO_2}-PE'_{CO_2}$) have been published: 0.61 kPa (Nunn and Hill, 1960), 0.46 kPa (Takki, Aromaa and Kauste, 1972), and 0.11 kPa (Whitesell et al., 1981).

In the absence of arterial hypotension, Whitesell and colleagues (1981) found that ($Pa_{CO_2}-PE'_{CO_2}$) remained constant during anaesthesia, and suggested that this difference could be quantified by one measurement of Pa_{CO_2}, this value being used to correct subsequent PE'_{CO_2} readings.

Perrin and co-workers (1983) showed that, while ($Pa_{CO_2}-PE'_{CO_2}$) may vary, for each patient the ratio Pa_{CO_2} to PE'_{CO_2} was constant. Thus, the use of the ratio $Pa_{CO_2}:PE'_{CO_2}$ could be used to derive

Pa_{CO_2} from measurements of $P\text{E}'_{CO_2}$. We applied both these methods to produce our indirect measurements of Pa_{CO_2}.

While this study was in progress, Kneeshaw, Harvey and Thomas (1984) reported an investigation of the use of the Bain system during Caesarean section. Their recommendation of an FGF of 120 ml kg^{-1} min^{-1} to maintain Pa_{CO_2} at 4.1–4.4 kPa may have been influenced by the fact that they included patients undergoing an emergency Caesarean section in whom carbon dioxide production is higher. Moreover, they did not measure Pa_{CO_2} directly.

Undoubtedly 70 ml kg^{-1} min^{-1} FGF was too low for patients undergoing elective Caesarean section. However, our prediction that preoperative values of Pa_{CO_2} could be maintained by increasing the FGF to 100 ml kg^{-1}min^{-1} was not fulfilled. Although Pa_{CO_2} was not measured before operation, it is unlikely that our study group would have had higher than the "normal" Pa_{CO_2} in pregnancy as no depressant premedication was administered. It is possible that the Pa_{CO_2} increased during the period of apnoea between induction and the commencement of IPPV. This period may have been unduly prolonged as elective lists are used for training our less experienced anaesthetists.

In the 100-ml kg^{-1} min^{-1} FGF group, the fact that the means of the final $P\text{E}'_{CO_2}$ and the derived Pa_{CO_2} altered little from initial values supports our view that the increase in FGF to 100 ml kg^{-1} min^{-1} is correct as far as carbon dioxide homeostasis is concerned. Perhaps a short period of manual hyperventilation after intubation would have reduced the Pa_{CO_2} to "normal", which would then have been maintained by an FGF of 100 ml kg^{-1} min^{-1}.

For absolute accuracy in estimating Pa_{CO_2} in pregnant women at term undergoing elective surgery, and being ventilated with a Mapleson E circuit, repeated blood-gas analyses are probably required. In clinical practice an FGF of 100 ml kg^{-1} min^{-1} will effectively avoid excessive hypo- or hypercarbia in most patients.

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ANAESTHESIA FOR EVACUATION OF RETAINED PRODUCTS OF CONCEPTION

Comparison between Alfentanil plus Etomidate and Fentanyl plus Thiopentone

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SUMMARY

Forty-four patients presenting for evacuation of retained products of conception were anaesthetized with either fentanyl and thiopentone, or alfentanil with etomidate, along with 70% nitrous oxide in oxygen. There was no difference between the two techniques in indices of immediate recovery (time to opening eyes and obeying a simple command), but the rate of return of higher mental functions (assessed by a coin counting test) was significantly better using the alfentanil–etomidate technique. There was no statistically significant difference between the techniques for apnoea or abnormal movements during anaesthesia, but alfentanil with etomidate was associated with significantly more pain on injection and a higher frequency of postoperative vomiting (40%).

In providing anaesthesia for the evacuation of retained products of conception it is desirable to avoid the use of the volatile inhalation agents because the induced relaxation of the uterus may increase blood loss from the uterus (Cullen, Margolis and Eger, 1970) and the risk of uterine perforation. To maintain anaesthesia, incremental doses of i.v. agents are used commonly, although this technique may cause prolongation of recovery after what is a short, but stimulating, procedure. This study was undertaken to compare the newer i.v. agents, alfentanil and etomidate with fentanyl and thiopentone. Quality of recovery and the frequency of side effects were assessed.

PATIENTS AND METHODS

Patients presenting for evacuation of retained products of conception after spontaneous inevitable abortion (within 16 weeks of gestation) were studied. No patient had received any sedative or analgesic medication before the study. Local ethics advisory committee approval was obtained, and the verbal consent of the patients was obtained after explanation. Recovery from anaesthesia was assessed using a modification of the coin counting test (Sikh and Dhulia, 1979). Ten coins, two of each denomination less than 50 pence, were used. Three coins were removed at random and the remaining seven coins presented in a column to the patient, who was instructed to pick them from the top of the column one by one, keeping a verbal running total as she did so, and the time taken from start to announcing the total value of the seven coins was noted. The patient was instructed to do this as quickly, but as accurately, as possible. If an incorrect total was reached, the test was repeated using a different random selection of seven coins. This test was performed once on the ward before operation, and twice in the postoperative period. The postoperative tests were performed under the same conditions as those undertaken before surgery: instructions were repeated exactly as before, with the patient sitting propped semi-upright to perform the test. All patients received metoclopramide 10 mg by mouth 90 min before operation and were then randomly allocated to receive either alfentanil and etomidate or fentanyl and thiopentone. When the patient arrived in the anaesthetic room, a 23-gauge

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Y-can (Wallace) was placed in a vein on the dorsum of the non-dominant hand, and the patient pre-oxygenated with three vital capacity breaths of 100% oxygen. The patient continued to breathe 100% oxygen until loss of consciousness. The fentanyl–thiopentone group were given fentanyl 1 μg kg^{-1} followed after 2 min by an induction dose of thiopentone (until loss of the eyelash reflex). The alfentanil–etomidate group received alfentanil 10 μg kg^{-1} followed immediately by an induction dose from a syringe containing etomidate 20 mg mixed with 1 ml of 2% lignocaine in an attempt to minimize pain on injection. (The 2-min delay was omitted because alfentanil has a more rapid onset than fentanyl.) If this dose was insufficient to cause loss of the eyelash reflex, induction was continued with etomidate alone. The induction dose and the time for induction were noted.

The patient was transferred immediately to the operating theatre, where she breathed 70% nitrous oxide in oxygen, and received incremental doses of thiopentone or etomidate as judged clinically necessary. All patients received syntocinon 10 mg; no patient received ergometrine. When the operation was finished, the nitrous oxide was discontinued and the patient breathed 100% oxygen for 10 breaths before being taken to the recovery area. The time of cessation of anaesthesia was noted as the time at which the nitrous oxide was discontinued, and the total incremental doses of drugs recorded. In the recovery area, the patient was asked (at 1-min intervals) to open her eyes, and the time since cessation of anaesthesia until she did so noted. Once the patient had opened her eyes, she was asked (at 1 min intervals until she did so) to show her left thumb, and the time since the cessation of anaesthesia was recorded. The coin counting test was administered at 15 and 30 min after the cessation of anaesthesia. Before the patient left the recovery area, she was asked if the injection was painful. Any occurrence of apnoea (longer than 30 s), abnormal movements during anaesthesia, or postoperative vomiting was noted.

RESULTS

Forty-four patients were studied, 22 in each group. One patient presenting for the study had to be excluded initially because of inability to count; no patient who performed the initial preoperative coin counting test had to be excluded subsequently for any reason. The results were analysed by Student's t test for patient weight, duration of procedure, time taken to perform the coin counting test, and by χ^2 distribution with Yates' continuity correction for the incidence of side effects.

There was no significant difference between the two groups for weight, duration of procedure or time to perform the preoperative coin counting test. The mean induction dose of thiopentone was 4.8 mg kg^{-1} (SD 1.2) and the incremental dose was 0.27 mg kg^{-1} min^{-1} (SD 0.13); the mean induction dose of etomidate was 0.32 mg kg^{-1} (SD 0.09) and the incremental dose was 0.02 mg kg^{-1} min^{-1} (SD 0.015). The results concerned with quality of recovery are shown in table I, and those concerned with incidence of adverse effects in table II. The alfentanil–etomidate group took significantly less time to perform the coin counting test at both 15 and 30 min following surgery than did the fentanyl–thiopentone group, but there was no significant difference between the two groups in time to opening eyes or showing left thumb on command. The alfentanil–etomidate group had a significantly greater frequency of pain on injection

TABLE I. *Quality of recovery. Results (mean(SD))*

					Time to perform coin counting test (s)		
						After op.	
	Weight (kg)	Duration (min)	Time to opening eyes (min)	Time to showing thumb on command (min)	Before op.	15 min	30 min
Fentanyl + thiopentone ($n=22$)	60.5 (6.7)	12.7 (4.3)	5.8 (3.8)	6.9 (3.9)	8.3 (2.6)	21.6 (15.4)	14.7 (8.1)
Alfentanil + etomidate ($n=22$)	58.9 (9.0)	11.9 (3.91)	4.13 (2.52)	4.13 (2.93)	8.2 (2.5)	12.3 (5.6)	9.9 (2.8)
Significance	ns	ns	ns	ns	ns	$0.01<P<0.025$	$0.01<P<0.025$

TABLE II. *Incidence of adverse effects. Results*

	Apnoea	Abnormal movements	Vomiting	Pain on injection
Fentanyl + thiopentone ($n = 22$)	7	0	2	1
Alfentanil + etomidate ($n = 22$)	2	3	9	10
Significance	ns	ns	$0.02 < P < 0.05$	$0.001 < P < 0.01$

(45% compared with 4.5%) and postoperative vomiting (40% compared with 9%). There were no significant differences between the two groups for frequency of apnoea or abnormal movements.

DISCUSSION

Of the common i.v. anaesthetic agents available, etomidate has pharmacokinetic properties that should make it suitable for use either in incremental techniques or when rapid recovery is needed. It has a considerably shorter elimination half-life (1–4.6 h) than thiopentone (5–12 h) (Goat, 1985), and shows no evidence of cumulation if given incrementally to maintain anaesthesia (Kay, 1976a). Similarly, alfentanil is better suited for short procedures or incremental use, with an elimination half-life of 1.63 h compared with that of 3.09 h for fentanyl (Bower and Hull, 1982), and a rapid onset of peak analgesia within 1 min, compared with 4 min for fentanyl (Niemegeers and Jansen, 1981). The combined use of an opiate allows a lower dose of i.v. anaesthetic agent to be used with shorter recovery times than when an i.v. anaesthetic agent is used alone (Horrigan et al., 1980). In addition, etomidate has been found to have too many adverse effects for use as a sole i.v. agent (Fragen, Caldwell and Brunner, 1976). The combination of alfentanil and etomidate should provide rapid recovery when i.v. agents are used to maintain anaesthesia.

Etomidate has a number of adverse effects which have limited its acceptance by anaesthetists: principally, pain on injection, abnormal movements during anaesthesia, and vomiting (Yelavich and Holmes, 1980). Various methods of minimizing these side effects have been tried, such as the concomitant use of an opiate and the injection of etomidate to a large vein in the antecubital fossa (Kay, 1976b).

The coin counting test (Sikh and Dhulia, 1979) was used as a method of assessing the quality of recovery. This was found to be a simple test to administer, and simultaneously tests a number of higher mental functions—sensory perception, visual acuity, ability to alter eye fixation quickly, fine muscular co-ordination, mental arithmetic and concentration. The use of sophisticated laboratory devices has shown that tests of recovery of consciousness do not correlate well with the persistence of impaired higher mental functions for several hours after anaesthesia, but the sophisticated apparatus is too bulky, expensive and complex for routine clinical use (Epstein, 1975). The coin counting test can be applied within the first 1 h after anaesthesia; the preoperative speed has been attained within 40–50 min after anaesthesia (Antonios, Inglis and Lees, 1984).

Speed of recovery

The results of the study show that immediate recovery (time to eye opening and showing left thumb on command) was not significantly different in the two groups, although the fentanyl–thiopentone group did take longer than the alfentanil–etomidate group. Similar findings have been reported by Kay and Venkataraman (1983), who also found that alfentanil with etomidate was not significantly superior to fentanyl and etomidate for immediate recovery, and by Hull and Jacobson (1983) using fentanyl or alfentanil with methohexitone.

Later recovery, assessed at 15 and 30 min after operation by the coin counting test was significantly better after alfentanil–etomidate than after fentanyl–thiopentone. Other workers have also found that differences between anaesthetic techniques may not be apparent if only immediate indices of recovery are studied (Simpson et al., 1976). Kay and Venkataraman (1983) found that late recovery, but not early recovery, was superior if alfentanil instead of fentanyl was used with etomidate. Other studies have also shown improved late recovery with alfentanil when compared with halothane to maintain anaesthesia

(Antonios, Inglis and Lees, 1984; Sanders, Sinclair and Sear, 1984).

Apnoea

All the patients in this study were pre-oxygenated with 100% oxygen because other studies had reported that alfentanil followed by methohexitone was commonly followed by apnoea (Cooper et al., 1983; Hull and Jacobson, 1983; Jellicoe, 1985). The results of this study showed no difference between the two groups, although fentanyl–thiopentone caused apnoea on a larger number of occasions than did alfentanil–etomidate. The lack of any respiratory depressant effects of etomidate may protect against this complication compared with the additional respiratory depressant effects of a barbiturate combined with the rapid onset of respiratory depression from alfentanil. No patient was apnoeic for more than 50 s.

Abnormal movements

Abnormal movements were not a problem in this study. Only three patients who received etomidate had any abnormal movements, and these were brief and occurred just after induction. Similar results have been obtained by Antonios, Inglis and Lees (1984), who used alfentanil before etomidate; only one of 25 patients had any abnormal movements. The occurrence of purposeful movements during surgery was interpreted as a sign of inadequate anaesthesia, and an incremental injection of thiopentone or etomidate was given.

Pain on injection

No patient complained spontaneously of pain during injection, but 10 patients, when questioned in the recovery area said the injection of etomidate had been painful. They had not been distressed by this, and it was usually described as a "slight sting". In this study, lignocaine was mixed with the etomidate in an attempt to minimize pain on injection. Alfentanil given before etomidate has been found to be effective in reducing pain on the injection of etomidate (although the site of the injection was not stated (Antonios, Inglis and Lees, 1984)), and Kay (1976b), reported that lignocaine used with etomidate was not effective in reducing pain on injection in paediatric practice. Kay and Cohen (1983) found that alfentanil preceding etomidate was better than fentanyl preceding etomidate in reducing pain, presumably because of the more rapid onset of peak analgesia with alfentanil. All injections in this study were to a vein on the dorsum of the hand. If etomidate is injected to a vein in the ante-cubital fossa, it is no more likely than thiopentone to be painful (Fragen and Caldwell, 1979).

Vomiting

The combination of alfentanil–etomidate caused significantly more postoperative vomiting than fentanyl–thiopentone (40 % compared with 9 %). This occurred immediately after the return of consciousness, was transient and no patient required anti-emetics in the postoperative period. Vomiting always stopped after a few minutes, and all patients were able to sit propped upright at 15 min without nausea to perform the coin counting test. Hull and Jacobson (1983) also found that similar patients given alfentanil with methohexitone were significantly more likely to vomit in the postoperative period than if given fentanyl with methohexitone.

CONCLUSION

It is concluded that the use of alfentanil and etomidate to induce and maintain anaesthesia will permit a more rapid return of higher mental functions than the combination of fentanyl and thiopentone, although the immediate indices of recovery (the time to opening eyes and obeying a simple command) were not different between the two techniques. Alfentanil given before etomidate was not associated with apnoea, and abolished the abnormal movements caused by etomidate. There was still significantly more pain on injection using the alfentanil–etomidate combination (40 %) compared with the fentanyl–thiopentone combination (4.5 %), although the pain was mild. The frequency of postoperative vomiting after alfentanil–etomidate was found to be over 40 %, compared with 9 % using the fentanyl–thiopentone combination. Although the vomiting was of short duration, was not followed by any nausea and did not affect the rapid return of higher mental functions, it is likely to limit the acceptance of the alfentanil–etomidate technique.

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ENFLURANE-INDUCED BURST FIRING OF HIPPOCAMPAL CA 1 NEURONES

In Vitro *Studies using a Brain Slice Preparation*

M. B. MACIVER AND S. H. ROTH

SUMMARY

Enflurane can produce seizure activity in the cortical EEG, in vivo, *at concentrations associated with surgical anaesthesia. The present study was designed to determine whether this seizure-like burst activity could occur in isolated cortical neurones. Enflurane altered synaptic transmission in the* in vitro *rat hippocampal slice preparation and produced seizure-like burst discharges of CA 1 neurones, at vapour concentrations equivalent to those obtained during anaesthesia (2–6 vol %; 0.5–1.5 mmol litre^{-1}). Burst discharges occurred both spontaneously and in response to stimulation of stratum radiatum fibres in the CA 1 pyramidal region, but not in the dentate area. Low concentrations of enflurane (approx. 0.75 mmol litre^{-1}), decreased the field potential responses of CA 1 neurones; however, dentate granule neurone responses were increased. Input/output analyses of field excitatory post-synaptic potential (EPSP) and population spike amplitudes revealed that the enflurane-induced depression of field potential responses was associated with decreases in synaptic input, whereas burst activity resulted from a decrease in the threshold of CA 1 neurones.*

EEG activation and seizure activity can be produced by cyclopropane (Mori, 1973), ether (Joas and Eger, 1971), ketamine (Bowyer and Winters, 1981) and enflurane (Black, 1979; Steen and Michenfelder, 1979). Of these, enflurane is the only agent in clinical use which produces seizure activity during anaesthesia (Persson, Peterson and Wahlin, 1978); it exibits a profile of excitatory and depressant CNS effects similar to those of phencyclidine, gamma-hydroxybutyrate, and alpha-chloralose (Winters, 1982). The convulsive actions of enflurane may result from excitation or depression, or both, in the CNS, since both have been observed during enflurane anaesthesia (Darimont and Jenkins, 1977; Steen and Michenfelder, 1979). Although the neurophysiological basis of anaesthetic-induced excitatory and convulsant effects is unknown, it is unlikely that a simple depression of neuronal excitability or synaptic transmission could account for all of the pharmacological actions of these agents (Roth, 1980; Richards, 1983).

A study using a chronic recording technique in cats demonstrated that enflurane-induced seizure activity was associated with concentration-dependent excitatory and depressant actions on reticular neurone firing, cortical evoked responses, and EEG activity (Stevens et al., 1984). Increases in brain stem firing activity and cortical responses were observed at sub-anaesthetic concentrations, while depression of reticular activity occurred at concentrations which produced surgical anaesthesia. In the cortical EEG, seizure activity was observed when reticular activity was depressed, although cortical evoked responses were enhanced (Stevens et al., 1984). These observations suggest that anaesthetic-induced seizure activity could be associated with either a release of brain stem inhibition or a direct excitation of cortical neurones.

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In the present study, the effects of enflurane were examined on the hippocampal brain slice preparation to determine whether this anaesthetic agent could produce activation and seizure-like activity in isolated cortical neurones. Effects on CA 1 pyramidal and dentate granule neurones were compared to determine whether the two populations of cortical neurones demonstrate different susceptibilities to anaesthetic-induced seizure activity. Such differential actions between CA 1 and dentate granule neurones would also provide support for selective, pathway-specific sites of action, as previously reported for other general anaesthetic agents (Roth, Bland and MacIver, 1983; Roth, Tan and MacIver, 1986).

Preliminary results have been published in an abstract (MacIver, Harris and Roth, 1984).

MATERIALS AND METHODS

Preparation

Experiments were conducted on 31 hippocampal slices; 18 for CA 1 responses, and 13 for dentate granule (DG) neurones. Rats were anaesthetized with ether, the heart stopped by a blow to the back of the thorax and the brain removed rapidly and placed in pre-cooled (10 °C) oxygenated artificial cerebrospinal fluid (CSF). Transverse slices (400 μm) of hippocampus were cut using a vibratome (Campden Instruments, U.K.), following dissection of the dentate–hippocampal formation. Slices were placed on a nylon mesh screen at the gas–liquid interface in a tissue chamber (Richards and Tegg, 1977). Oxygenated (95% oxygen–5% carbon dioxide), prewarmed (35 °C) CSF was continuously perfused through the bath at a rate of 1–1.5 ml min^{-1}.

Electrode placement

A bipolar nichrome stimulating electrode was placed on perforant path fibres or in the stratum radiatum to activate excitatory synaptic inputs to DG or CA 1 pyramidal neurones, respectively (fig. 1). Similarly, antidromic responses were produced by stimulation of the alveus or mossy-fibre pathways. Extracellular recording electrodes (sodium chloride 2 mol litre^{-1}, 2–10 MΩ) were placed in the cell body regions of DG and CA 1 areas to record synaptically evoked field potentials (FP) and unit discharge activity. Paired stimulus pulses of 0.01–0.05 ms duration (25–70 μA) were

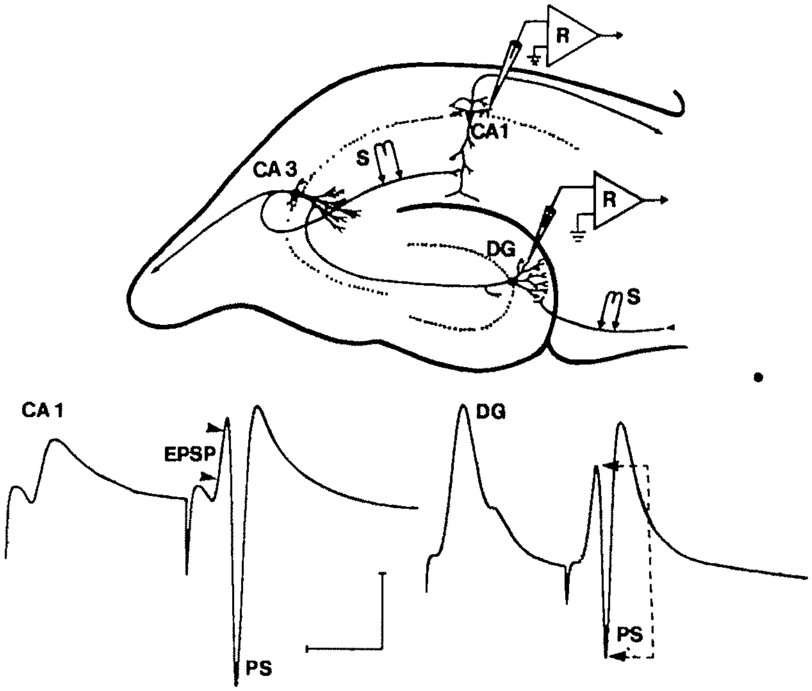

FIG. 1. Diagram of a hippocampal slice showing placement of stimulating (S) and recording electrodes (R). Sample recordings from CA 1 and DG demonstrate paired pulse potentiation in both pathways. Arrows indicate portions of recordings used to determine EPSP slope (dV/dt) and population spike (PS) amplitude. Calibration: 2.0 mV and 10 ms.

delivered at 0.1 Hz. Stimulus intensity was varied to determine input/output relationships at a fixed interstimulus interval of 25 ms (Andersen et al., 1980; Abraham, Bliss and Goddard, 1985). In addition, interpulse interval delays were varied between 5 and 120 ms, in 5-ms increments, to examine the time course of short-term potentiation as a measure of synaptic facilitation and local inhibition. Recorded signals were amplified (× 1000), filtered (1 Hz to 10 kHz, bandpass), and stored digitally for later analysis. Population spike (PS) amplitudes were measured from threshold to peak negativity and excitatory post-synaptic potential (EPSP) rise times (dV/dt) were measured on the initial EPSP slope (fig. 1). Rise times were determined by linear regression analysis of data between 20 and 80 % of the EPSP peak positivity.

Administration and analysis of enflurane

Enflurane was applied as a vapour to the tissue chamber via the prewarmed and humidified oxygen–carbon dioxide gas stream above the brain slices, using a calibrated commercial vaporizer (Ohio Medical Products, Madison, Wis.). Concentrations, expressed as volume percent (vol %), refer to settings on the vaporizer dial. Anaesthetic concentrations equivalent to minimum alveolar concentrations required to maintain anaesthesia (MAC = 2–4 vol %) (Stevens et al., 1984) were used. To reach equilibrium, vapour concentrations were applied for a minimum period of 30 min. Accurate measurements of enflurane concentrations in the perfusate were obtained using a Hewlett-Packard 5880A gas chromatograph fitted with a glass column, packed with Poropak Q, and a flame ionization detector. The carrier gas was nitrogen delivered at a flow rate of approximately 40 ml min^{-1}. Temperatures of the injector, oven and detector were 155, 140 and 170 °C, respectively. Test samples (20 μl) were taken from the recording chamber with a gas-tight Hamilton syringe and injected directly to the column. Peak: area ratios from the test samples were plotted against those from known standards to determine bath concentrations (fig. 2). Dextrose was used as an internal standard in the artificial CSF. Column retention times were approximately 3.5 and 7.5 min for enflurane and dextrose, respectively.

Materials

Adult male Sprague–Dawley rats (200–300 g) were obtained from the University of Calgary Biosciences Vivarium. Enflurane was obtained from Ohio Medical Products (Pointe Claire, Que.). The artificial CSF physiological solution had the following composition (mmol $litre^{-1}$): NaCl 134; KCl 4.5; $CaCl_2$ 1.6; KH_2PO_4 1.25; $MgSO_4$ 2; $NaHCO_3$ 16; dextrose 10 (modified from Richards, Russell and Smaje (1975)). Calcium and potassium concentrations were adjusted to the approximate values measured *in vivo* (Krnjevic, Morris and Reiffenstein, 1982).

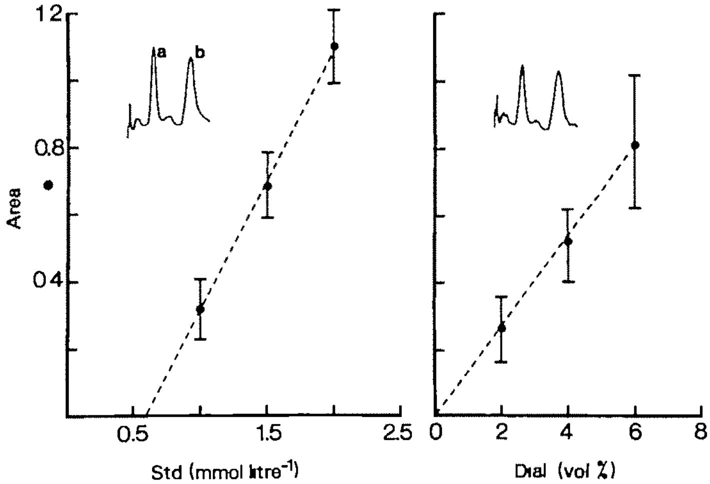

FIG. 2. Linear relationships between standard concentrations (Std), vaporizer dial settings (Dial) (vol %) and integrated peak area ratios (Area) are shown. Each point is the mean ±SD of at least four determinations. Examples of gas chromatograph recordings are shown in the insets for 1.5 mmol $litre^{-1}$ STD and 4.0 vol % samples (peak a = enflurane; peak b = dextrose).

RESULTS

Enflurane-induced burst activity

Figure 3 shows typical recordings from CA 1 and DG regions during enflurane-induced field bursts. CA 1 burst discharges were concentration-dependent, with low concentrations (0.5–2.0 vol %; 0.5–0.9 mmol litre^{-1}) producing only small amplitude discharges, and higher concentrations (2.5–5.0 vol %; 1.0–1.3 mmol litre^{-1}) producing large amplitude field bursts which increased in frequency. Both spontaneous and stimulus-evoked burst activities were observed in the CA 1 area. Burst discharges were periodic and did not occur in response to each stimulus. Instead, burst activity occurred intermittently throughout the period of exposure to enflurane. Spontaneous burst discharges were not observed in DG neurones, and perforant path evoked responses appeared relatively normal at concentrations of enflurane which produced marked seizure-like activity in the CA 1 area. Enflurane-induced burst firing of CA 1 neurones could, occasionally, be recorded in the dentate area (volume conduction), and resulted in a late "ringing" of the perforant path to DG neurone evoked responses which occurred 15–20 ms after the DG population spike (figs 3 and 4). These late responses appeared to be CA 1 neurone bursts which were synchronized with the perforant path stimulus (fig. 3), perhaps triggered via DG neurone activation of CA 3 neurones which subsequently synapse onto CA 1 cells (Andersen, 1975), or via direct perforant path activation of CA 1 neurones. CA 3 neurone firing patterns were not altered in the presence of enflurane (data not shown; three experiments), and multiple fibre-volleys were not recorded in stratum radiatum at concentrations which produced spontaneous or evoked seizure discharges in CA 1 neurones. Multiple firing of DG neurones was never observed, even in the presence of vapour concentrations which produced increased field potential responses (for example: 0.5–2.5 vol %; 0.5–1.0 mmol litre^{-1}). Thus, enflurane-induced seizure activity appeared to be localized to the CA 1 region; however, a more detailed study of CA 1 and CA 3 responses is required to determine how perforant path activation may result in CA 1 neurone burst firing.

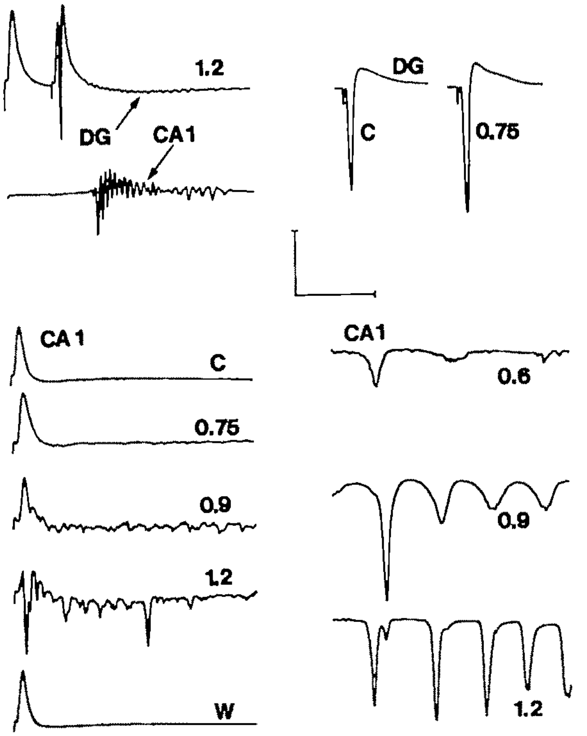

FIG. 3. Upper left: perforant path evoked field potential responses recorded from DG and CA 1 neurones from the same slice are shown in the presence of enflurane 1.2 mmol litre^{-1}. The late "ringing" of DG responses (arrow) corresponds with burst firing in CA 1 (arrow). Lower left: field EPSP responses evoked by low intensity stimulation of stratum radiatum are shown for control (C), and in the presence of enflurane. Depression of EPSP amplitude and field bursting were concentration dependent and reversible on washout (W). Upper right: antidromic field potentials from DG neurones are shown for control (C) and in the presence of enflurane. Lower right: spontaneous field bursts recorded from the CA 1 region were also concentration dependent. Concentrations shown are in mmol litre^{-1}; calibration · 5 mV, 40 ms (left), 20 ms (right).

Analysis of field potentials

A characteristic field potential was recorded from the cell body layers when input fibres to either DG or CA 1 cells were electrically stimulated. Weak stimuli (10–15 µA) produced a positive waveform (field EPSP) which originated from the synchronous depolarization of postsynaptic neurones in response to the release of transmitter from input fibres (fig. 1) (Andersen, Blackstad and Lomo, 1966; Langmoen and Andersen, 1983). When the intensity of the stimulation was increased or potentiation occurred, or both, the positive waveform increased in amplitude and a negative spike appeared superimposed on the EPSP (compare responses to 1st and 2nd stimulus pulses in figure 1). This negative waveform reflects the synchronous discharge of postsynaptic neurones (Andersen, Bliss

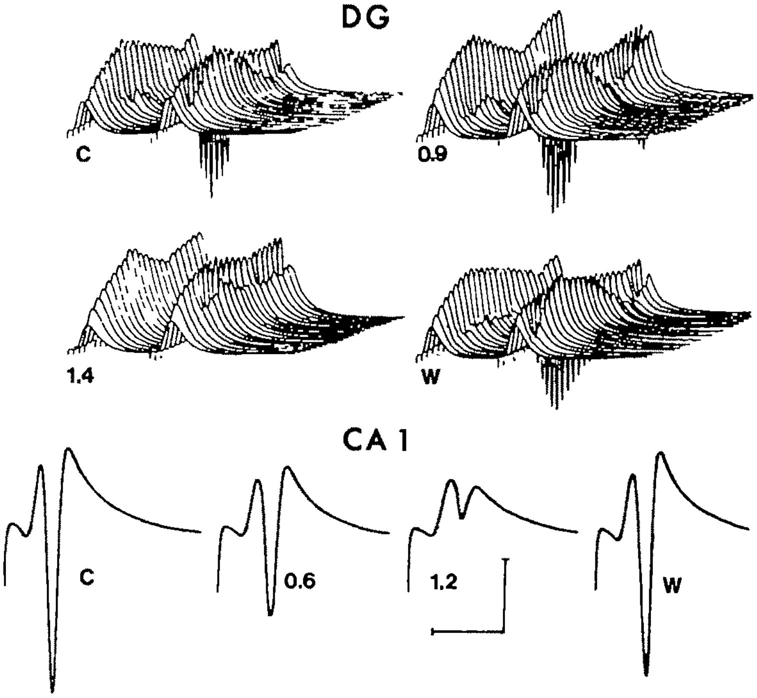

FIG. 4. DG: Multiple sweeps of field potentials produced by perforant path inputs to DG neurones at various stimulus intensities. These data were used for the input/output curve in figure 5. In the presence of enflurane 0.9 mmol litre^{-1} both EPSP and PS amplitudes were increased. At greater concentrations (1.4 mmol litre^{-1}) PS responses were depressed, although EPSP amplitudes remained above control. On washout (W), responses returned to control (C) values. CA 1: Enflurane depressed both the EPSP and PS of stratum radiatum to CA 1 evoked field potentials. Calibration: 5 mV and 20 ms (DG), 10 ms (CA 1).

and Skrede, 1971; Bliss and Richards, 1971). The relationship between the positive synaptic potential (EPSP) and the amplitudes of the negative population spike (PS) describes an input/output function (E–S curve) for the pathway (Richards and White, 1975; Andersen et al., 1980; Abraham, Bliss and Goddard, 1985). The intercept on the EPSP axis provides a measure of postsynaptic discharge threshold, and the slope of the curve describes depolarization–excitation coupling (fig. 5) (Lomo, 1971; Richards, Russell and Smaje, 1975; Abraham, Bliss and Goddard, 1985).

Effects of enflurane on evoked field potentials

Enflurane produced concentration-dependent biphasic effects on perforant path to DG evoked field potentials, but only a monophasic depression of CA 1 responses. Low concentrations (0.5–2.0 vol %; 0.5–0.9 mmol litre^{-1}) produced a facilitation of transmission in DG, while higher concentrations (2.5–4.0 vol %; 0.5–1.2 mmol litre^{-1}) produced depression. Half-maximal (ED_{50}) depression of perforant path inputs occurred at approximately 3.0 vol % (1.0 mmol litre^{-1}) Stratum radiatum to CA 1 evoked responses appeared to be more sensitive to the depressant actions of enflurane, since half-maximal effects occurred at 2.0 vol % (0.9 mmol litre^{-1}) (fig. 4).

Depression of stratum radiatum inputs to CA 1 neurones appeared to involve synaptic actions, because reductions in PS amplitudes were always accompanied by depression of synaptic potentials (fig. 4). In the dentate area, in contrast, enflurane produced a depression of PS responses which was not accompanied by decreases in EPSP amplitudes, suggesting a predominantly postsynaptic site of action (see input/output analysis below). Conversely, in both the CA 1 and DG areas, response latencies were increased in the presence of all effective concentrations of enflurane, including the lowest which increased the amplitude of the DG neurone field potential. Effects on field potential responses appeared to be independent of

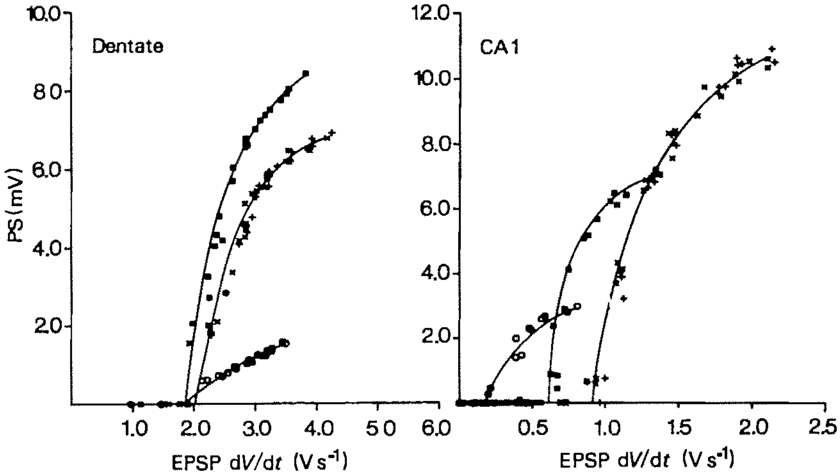

FIG. 5. The relationship between EPSP rise time (dV/dt) and PS amplitude demonstrates the differential actions of enflurane on dentate and CA 1 areas. Perforant path to dentate responses were increased by low concentrations (■) and depressed by higher concentrations (○). These effects appeared to involve postsynaptic sites of action, since similar degrees of synaptic depolarization (EPSP) resulted in different PS amplitudes. In contrast, enflurane altered both the EPSP and PS responses recorded from CA 1 neurones (see text). The shift to the left of the EPSP axis intercept indicated a direct excitation (decreased threshold) of CA 1 neurones was produced by enflurane. + = Control; × = wash; ■ = 0.9 mmol litre^{-1}; ○ = 1.4 mmol litre^{-1}.

stimulus intensity for both pathways studied (data shown for DG responses in figure 4). Thus, enflurane-induced enhancement or depression of responses occurred to the same extent at both low and high degrees of stimulation, indicating that recruitment of afferent fibres was not affected.

The effects of enflurane on evoked potentials in both CA 1 and DG areas were often associated with increased background unit firing activities (not shown). Recording electrodes were located below the cell body layers where basket cell inhibitory interneurone somas are most prevalent (Schwartzkroin and Knowles, 1983). This, together with the observation that firing activities tended to be grouped into short bursts which are characteristic of basket cell firing (Schwartzkroin and Knowles, 1983), suggests that increases in background discharge may be partially attributed to enflurane-induced activation of inhibitory interneurones (see also Latency Analysis below).

Enflurane effects on input/output relationships

To determine whether enflurane altered postsynaptic responses, input/output analyses of the two synaptic pathways were performed. This method of analysis involves a comparison of the strength of synaptic input with the amplitude of postsynaptic response (output), termed E–S curve analysis (Andersen et al., 1980). Rate of rise (dV/dt) of the field EPSP does not correlate directly with the apparent EPSP amplitude (compare figures 4 and 5); however, dV/dt provides a better measure of synaptic input for two reasons. First, responses are measured before possible alteration by postsynaptic currents contributing to discharge and in response to polysynaptic drive (Turner, Richardson and Miller, 1984). Second, the rate of rise of the EPSP is known to correlate better with discharge probability than EPSP amplitude and is commonly used for this type of analysis (Abraham, Bliss and Goddard, 1985). As shown in figure 5, a steep relationship between EPSP and PS occurred at low stimulus intensities, whereas PS responses approached a maximum at higher intensities (see also: Andersen et al., 1980; Ault and Nadler, 1983).

In the presence of enflurane 0.75 mmol litre^{-1}, PS amplitudes in DG were increased, although perforant path EPSP dV/dt responses were slightly reduced; thus, for a given amount of synaptic input, postsynaptic discharge was increased (fig. 5). This suggests that, in the DG area, postsynaptic facilitation underlies the enhancement of transmission observed at these low concentrations. In the presence of enflurane 1.2 mmol litre^{-1}, however, PS failure was almost complete, although EPSP dV/dt responses were not markedly depressed. Higher concentrations (1.4 mmol litre^{-1}) produced complete depression of the PS, and decreases in EPSP dV/dt and amplitude (data not shown). Thus, the excitatory actions on perforant path inputs appear to involve primarily postsynaptic sites. Synaptic responses (EPSP) were only depressed in the presence of concentrations greater than those required to block postsynaptic discharge.

In contrast to DG neurone responses, enflurane-induced depression of CA 1 field potentials was associated with reduced EPSP responses. Figure 5 shows that depression of field potentials was accompanied by increased excitability (decreased threshold) in the CA 1 area; that is, a given EPSP produced larger PS responses in the presence of the anaesthetic. Field potential amplitudes, however, were not increased above control values because the EPSP responses which accompanied PS facilitation were smaller. It is difficult to attribute field potential depression to a postsynaptic failure given the observed increase in CA 1 pyramidal cell excitability. Furthermore, all effective concentrations produced a depression of the stratum radiatum EPSP dV/dt and this appeared to be the major mechanism underlying the depression of the field potential. Depolarization–discharge coupling did not appear to be altered until relatively high concentrations were applied (> 1.0 mmol litre^{-1}). Fibre-volley amplitudes were not affected by low concentrations; however, concentrations which produced greater than 90% depression of EPSP amplitudes were accompanied by small reductions in fibre-volley amplitudes in both the CA 1 and DG areas.

Effects on antidromic field potentials

Antidromic responses were used as a measure of enflurane effects on electrical excitability of DG and CA 1 neurones. Concentrations which produced enhanced perforant path to DG responses also increased dentate antidromic responses (fig. 3). Depression of antidromic spike amplitudes required concentrations greater than 5.0 vol % (1.3 mmol litre^{-1}), which reduced synaptic transmission by greater than 90%. Multiple antidromic discharges were produced in the CA 1 area when spontaneous and synaptically evoked seizure activity was present; however, antidromic bursts were not observed in the DG area.

Latency analysis

Latency analysis was used to examine effects on paired pulse potentiation and local synaptic inhibition. Potentiation was measured by applying paired pulses which were subthreshold for a PS response on the first pulse. The amplitude of the PS produced in response to the second pulse was measured, as shown in figure 6. Latency profiles were constructed by plotting the amplitude of PS responses, at various interstimulus intervals. Optimal intervals of 30 ms for CA 1 and 25 ms for DG control responses were observed. In the presence of enflurane, paired pulse potentiation still occurred and enhanced potentiation was associated with increased response amplitudes produced by low concentrations in the DG area;

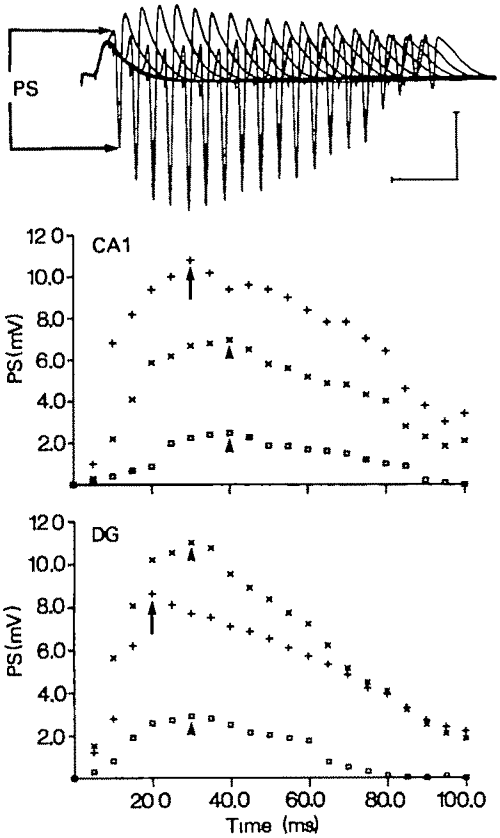

FIG. 6. Upper: 20 superimposed recordings of stratum radiatum to CA 1 evoked responses are shown at various interstimulus intervals. PS amplitude measurements (indicated by arrows) were used for subsequent paired pulse latency plots. Lower: enflurane decreased CA 1 PS amplitudes and shifted the control (+) optimal latencies of 30 ms (arrow) to 40 ms in the presence of the anaesthetic (arrowheads; × = 0.75 mmol litre^{-1} □ = 1.2 mmol litre^{-1}). A similar shift in optimal latencies was observed for DG neurone responses at concentrations which enhanced (×; 0.75 mmol litre^{-1}) or depressed (□: 1.2 mmol litre^{-1}) PS amplitudes. Calibration: 4 mV and 20 ms.

reduced potentiation accompanied depression of responses in both pathways. Low concentrations also appeared to enhance inhibition in both pathways and higher concentrations resulted in further enhancement of late inhibition in DG neurones, with no additional effect in the CA 1 area. Increased inhibition was observed as a prolongation of the early component (optimal interstimulus intervals were shifted from 30 to > 40 ms) and steeper tailing in late responses. This interpretation of latency responses is supported by earlier observations which demonstrated similar effects produced by GABA and pentobarbitone (MacIver and Roth, unpublished observation; Gribkoff and Ashe, 1985; Ashton and Wauquier, 1985). Pentobarbitone has also been shown to enhance local inhibition in the hippocampal formation (Nicoll et al., 1975).

DISCUSSION

The results agree with recent (Stevens et al., 1984) and earlier (Darimont and Jenkins, 1977; Black, 1979) observations in mammalian *in vivo* preparations. These studies reported both excitatory and depressant actions of enflurane on CNS electrical activity. Our results extend these observations to include a cortical site of action for biphasic and convulsive effects of enflurane, since ascending afferent systems are not operative in the *in vitro* brain slice preparation. Drug effects on ascending inputs to cortical centres may exacerbate seizure-like actions in hippocampal and neocortical areas, *in vivo*. The present results demonstrate the intrinsic seizure susceptibility of the hippocampal formation and relate these anaesthetic-induced effects to actions at a neuronal level.

Enflurane did not appear to depress synaptic inhibition in either DG or CA 1 pathways; instead, enhanced inhibition was apparent from the paired pulse latency analysis. Increases in background firing activity of inhibitory interneurones also suggests an enhancement of inhibition. Stevens and co-workers (1984) noted that multiple unit activity in brainstem regions could be increased by enflurane, which may reflect a generalized stimulatory action on neuronal excitability in the CNS. Enflurane appeared to increase postsynaptic excitability in both CA 1 and DG regions, since increases in PS amplitudes were observed in response to equivalent EPSP input (fig. 5). Similar excitatory effects have been observed in the presence of other volatile anaesthetics *in vivo* (Winters, 1982).

Enflurane-induced burst firing

The seizure-like actions produced by enflurane were correlated with decreases in the threshold for discharge of CA 1 neurones. This was particularly evident from input/output analysis of recordings in the CA 1 region (fig. 5). All effective concentrations produced a shift to the left in the input/output relationship, indicating that less synaptic input was required to produce postsynaptic discharge. This shift in the intercept of the stratum radiatum EPSP axis is consistent with a decrease in threshold of the CA 1 neurones, and would be expected to accompany enflurane-induced spontaneous burst firing. A direct excitation of pyramidal neurones appears to be the most likely mechanism of enflurane-induced seizure activity in the present study, and has been previously postulated to underly the epileptogenic effects of kainate and folate (Olney, Fuller and deGubareff, 1981; Clifford and Ferrendelli, 1983). By comparison, DG neurone excitability did not appear to be altered by enflurane, since a shift in the intercept of the perforant path EPSP axis was not observed (fig. 5). This is consistent with a lack of enflurane-induced seizure activity in the dentate area. Enflurane-induced increases in DG field potential responses appear to be produced via a postsynaptic effect, since equivalent EPSP input resulted in larger PS amplitudes; however, this enhanced response was not associated with a lower threshold for discharge.

Differential sensitivity of hippocampal regions

Inputs to CA 1 neurones were altered by the lowest vapour concentrations of enflurane; significant depression occurred in this pathway, although DG responses remained virtually unchanged or enhanced. This differential sensitivity cannot be explained on the basis of drug distribution or kinetics, since the concentrations at these sites should be similar in thin (400-µm) slices of tissue. Furthermore, the onset times of the effects for the two pathways were identical and rapid (< 60 s). We propose that differences in drug efficacy are the result of a differential localization or composition, or both, of sites of action in the pathways studied. It is well known, for example, that DG neurones are less sensitive to the actions of other convulsants than the pyramidal regions of the hippocampus, and this may reflect dominant inhibitory mechanisms in the DG area (Schwartzkroin, 1983). Recent studies of penicillin and GABA antagonist actions on DG neurones also demonstrated a relatively high resistance to convulsant-induced burst firing (Fricke and Prince, 1984), which was attributed to the apparent lack of inward calcium currents in these cells. CA 1 and CA 3 neurones are also more sensitive than DG cells to the non-specific effects produced by anoxia and mechanical damage (Kelly, 1982; Lipton and Whittingham, 1979). These latter two forms of perturbation produce seizure activity which is similar to that produced by enflurane; however, important differences are apparent. Anoxia and mechanical damage, for example, produced irreversible or only partially reversible alterations (Whittingham, Lust and Passonneau, 1984), whereas the effects of enflurane were readily reversible. Furthermore, enflurane-induced seizure activity tended to be intermittent, and burst responses did not correlate directly with the intensity of stimulation. Anoxic burst responses, in contrast, increased at higher intensities of stimulation and occurred in response to each stimulus (MacIver and Roth, unpublished observation; Schwartzkroin 1983).

In summary, we have demonstrated that enflurane produced excitatory and depressant effects at a synaptic level *in vitro*. The biphasic responses, previously observed *in vivo*, can include alterations of both neuronal excitability and synaptic transmission at cortical sites. Seizure-like activity appeared to be correlated with direct excitation of CA 1 neurones. Stratum radiatum to CA 1 evoked responses were depressed by enflurane via actions at a synpatic level. DG neurones, in contrast, did not produce burst firing and the biphasic (excitation–depression) responses appeared to involve postsynaptic sites of action. The differential effects produced on DG and CA 1 neurones also provide further evidence that anaesthetic sites of action are selective (Roth, 1980) and pathway specific (Roth, Bland and MacIver, 1983).

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DIFFERENTIAL NERVE BLOCKADE: ESTERS *V*. AMIDES AND THE INFLUENCE OF pK_a

J. A. W. WILDSMITH, A. J. GISSEN, B. TAKMAN AND B. G. COVINO

SUMMARY

The in vitro *sensitivities to local anaesthetic blockade of A, B and C fibres in rabbit vagus nerves were examined using a series of structurally similar amide agents, which varied in lipid solubility and anaesthetic potency. The actions of these drugs were compared with one another, and with those of a series of amino-ester local anaesthetics studied previously. The results demonstrated that A fibres are the most, and C fibres the least, sensitive to blockade by local anaesthetic agents. As with the ester drugs, equipotent concentrations of the amides blocked C fibres at approximately the same rate, but the absolute and relative rates of development of A fibre blockade were related to lipid solubility. As the latter increased, so did the rate of A fibre blockade. Combining the results of the two studies suggests that an agent of low lipid solubility and high pK_a might be used to produce differential C fibre blockade. Comparison of the results obtained with the two different classes of drug indicates that the ester structure may have an inherently more potent action than the amide.*

All the clinically useful local anaesthetic drugs have a common basic molecular structure: an aromatic ring is connected to an amine group by an intermediate chain. The latter includes either an amide or an ester bond, and side chains may be added to any part of the molecule. The differences in drug profile which these variations in molecular structure produce may be related to their effects on physico–chemical properties—notably lipid solubility and pK_a. Absolute potency, for example, increases with lipid solubility (Covino, 1980).

A study of the differential nerve blocking activity of a series of analogues of the ester-linked agent, procaine, showed (using an *in vitro* rabbit vagus nerve preparation) that an agent's lipid solubility affected also the relative rates at which different types of nerve fibre were blocked (Wildsmith et al., 1985). The small, slowly conducting C fibres were blocked at much the same rate by equipotent concentrations of all agents. The large, rapidly conducting A fibres were blocked at a faster rate than the C fibres by an agent of high lipid solubility, but more slowly than the C fibres by an agent of low lipid solubility. The present study was undertaken to determine whether the same was true of a series of amide-linked agents, and to allow comparison of the *in vitro* activities of the two groups of drugs.

MATERIALS AND METHODS

Experiments were performed under exactly the same conditions using the same apparatus as in the previous study of ester-linked agents. Full details of methodology have been published (Wildsmith et al., 1985); only a brief summary will be given here.

The cervical vagus nerves of 2-kg albino rabbits were removed, desheathed and mounted in an airtight nerve chamber at room temperature. The apparatus allowed stimulation of the nerve and recording of the resultant compound action potentials for A, B and C fibres. A 1-cm section of the nerve was exposed to a submaximal blocking concentration of a drug (dissolved in a carbonated-Liley solution at pH 7.4 ± 0.02) until the changes in the height of the action potentials were stable.

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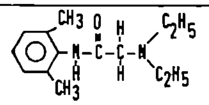
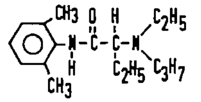
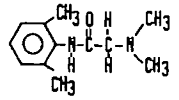
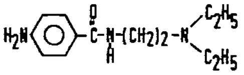
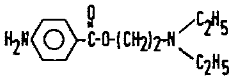
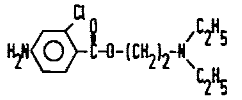
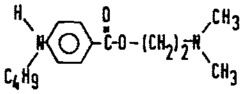
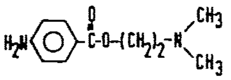
Drug	Structure	pK_a	C'log P
Lignocaine		7.7	2.24
Etidocaine		7.7	3.37
W36017		7.4	1.35
Procainamide		9.3	1.19
Procaine		9.0	2.32
Chloroprocaine		9.0	2.94
Amethocaine		8.5	3.73
dl-MAPA		8.7	1.42

FIG. 1. Chemical formulae of the drugs used, their pK_a values and the calculated indices of their base forms (C'log P). The drugs below the dotted line were examined in the previous study.

Photographs of the action potentials, as displayed on oscilloscope screens, were taken onto polaroid film to allow measurement of the degree of blockade (defined as percentage decrease in the height of the action potential) at appropriate intervals. Dose–response relationships were constructed by plotting the maximal effect on each fibre type against drug concentration using logarithmic–probit graph paper. In addition, linear plots of the changes in the amplitudes of the compound action potential with time (rate of block) were constructed.

The drugs studied were the hydrochloride salts of lignocaine, etidocaine and W36017 (fig. 1). Linear regressions of the log of drug concentration against probit score were derived for the effect of each drug on each fibre type and solved for the point of 50% depression of the action potential amplitude (ED_{50}). The standard error (SE) of that value was also obtained. The relationship between potency (ED_{50}) and lipid solubility was examined by linear regression analysis on a log–log plot. C'log P, a calculated octanol/water partition coefficient for the *base* form of the drug (Hansch and Leo, 1979), was used as the index of lipid solubility and was plotted against the concentration of the base form of the drug which would be present at its ED_{50} at pH 7.4. This was derived using the formula:

$$ED_{50}\,[\text{base}] = ED_{50}\,[\text{total}]\,\frac{1^{\mathrm{pH}-\mathrm{p}K}}{1+1^{\mathrm{pH}-\mathrm{p}K}}.$$

Statistical analyses were performed using analysis of covariance.

RESULTS

Figure 2 illustrates the dose–response relationships for the three drugs on A, B and C fibres drawn on a log-probit plot. Table I shows the ED_{50} for each drug on each fibre type, together with the SE and the number of experiments used to obtain these data. For each drug, the ED_{50} for A fibres was less than that for B fibres, which was lower than that for C fibres. The slopes of the dose–response relationship were steeper for A than B, and steeper for B than C fibres.

Figure 3 shows the percent changes in the compound action potentials for A and C fibres plotted against time in two individual investigations involving approximately equipotent concentrations of etidocaine and lignocaine. Etidocaine blocked A fibres more rapidly than C fibres in this, and every other, investigation. Lignocaine blocked A and C fibres at much the same rate. In the example shown, the initial rate of C fibre blockade was very slightly faster than A, but the reverse was true in other investigations. In most studies with W36017, the initial rate of C

TABLE I. *ED_{50} (mmol litre^{-1}) (and its standard error) for the effect of each drug used on each fibre type.* n = *Number of experiments*

Fibre type	Etidocaine	Lignocaine	W36017
A	0.019(0.004)	0.108(0.039)	0.675(0.111)
n	6	6	6
B	0.028(0.010)	0.157(0.066)	0.965(0.297)
n	7	7	5
C	0.054(0.024)	0.267(0.136)	1.50 (0.686)
n	7	7	6

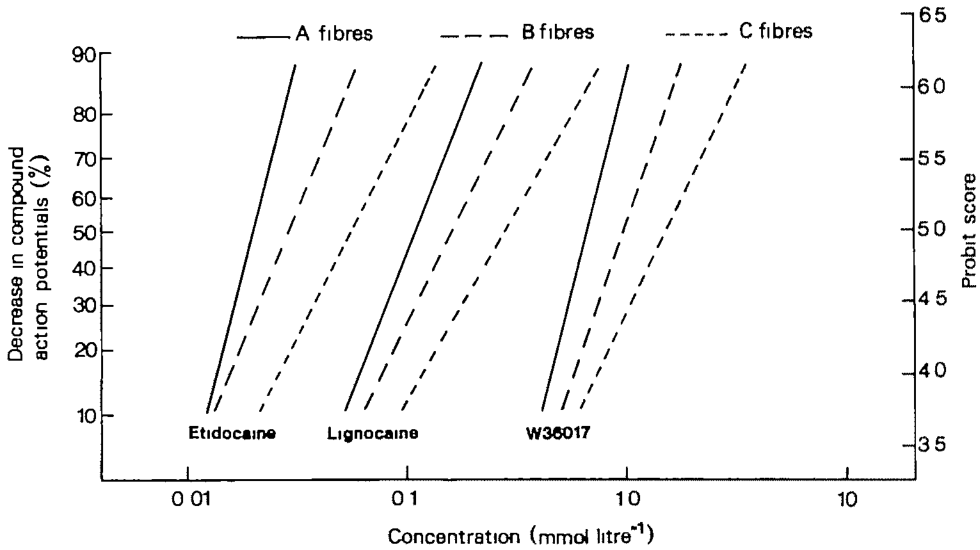


FIG. 2. Dose–response relationships for the effect of three amide local anaesthetics (lignocaine and two analogues) on three fibre types. Desheathed rabbit vagus *in vitro*; carbonated Liley solution; 23–26 °C; pH 7.4.

fibre blockade was faster than A (see figure 5), but this was not a consistent finding.

Figure 4 shows the plot of $C'\log P$ against ED_{50} [base] for A fibres on a log scale. Data for both the amides studied here, and for the procaine analogues studied previously, are included.

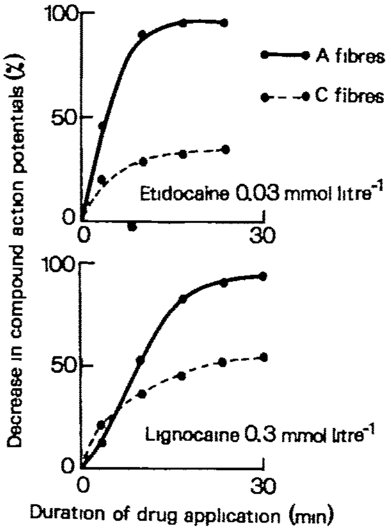


FIG. 3. Percent decreases with time in the compound action potentials for A and C fibres when exposed to etidocaine 0.03 mmol litre^{-1} and lignocaine 0.3 mmol litre^{-1}.

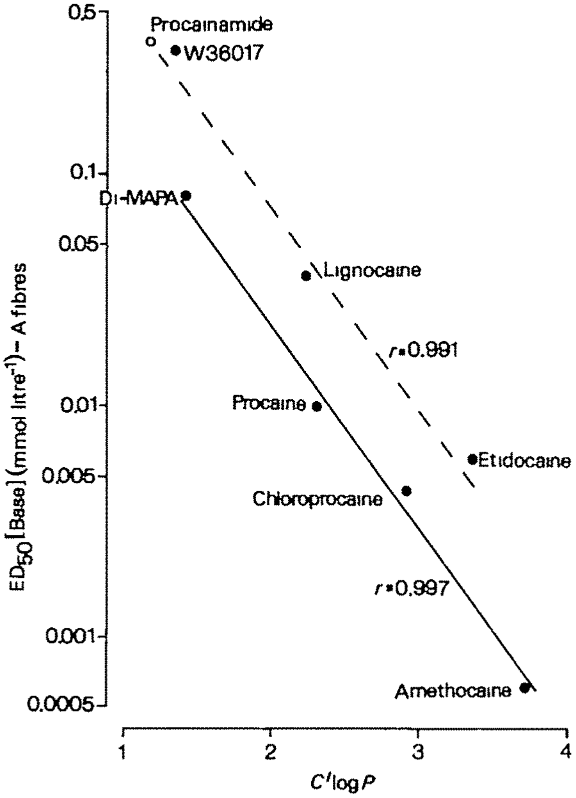


FIG. 4. Relationship between ED_{50}[Base] and calculated lipid solubility.

Analysis of covariance showed no significant difference in the slopes of the fitted lines for esters and amides, and a model with parallel lines was, therefore, fitted. This showed a significant difference in the intercepts of the two lines ($P < 0.01$), indicating that esters are more potent than amides at any given value of lipid solubility. Analysis of covariance was also used to test whether the figure for procainamide differed significantly from the relationship for amides ($P < 0.95$) or esters ($P < 0.1$). This confirms the impression from the figure that procainamide fits the amide line well, but the ester line poorly. Similar plots may be obtained using the ED_{50} figures for B and C fibres.

DISCUSSION

The results of this study confirm previous work (Gissen, Covino and Gregus, 1980) that the *in vitro* sensitivity to local anaesthetic blockade of the fibres in the rabbit vagus nerve is in the order A > B > C (fig. 2, table I) once stable equilibrium blockade has been established. The results also indicate that the potency/lipid solubility of amide local anaesthetic drugs had a similar effect on the rate of development of *in vitro* differential fibre blockade, as it did with the ester-linked agents (Wildsmith et al., 1985). The very potent agent, etidocaine, clearly blocked A fibres at a faster rate than C fibres. This suggests that such a highly lipid soluble agent was able to penetrate easily the very considerable lipoprotein coverings around A fibres to demonstrate rapidly their greater basic sensitivity to blockade. The other two amide agents blocked both types of fibre at approximately the same rate. Because of their lower lipid solubility, they would have taken longer than etidocaine to penetrate the A fibre diffusion barriers, so that the onset of blockade of those fibres was delayed somewhat. C fibres are surrounded by little in the way of diffusion barriers and, consequently, they were blocked by equipotent concentrations of each drug at much the same rate.

As with the ester agents, the absolute potency of the amides correlated well with lipid solubility. However, comparison of the results of the two studies (fig. 4) has suggested that there is a difference in basic potency between the two types of drug. Calculations based on the 95% confidence limits of the regression lines for the two types of drug indicate that an ester will have an ED_{50} between one-half and one-sixth that of an amide of equal lipid solubility. In fact, it is often believed that the amide drugs are the more potent, but this is the result of the differences in pK_a between the two groups (fig. 1). At physiological pH, much greater proportions of the un-ionized, lipid soluble form of an amide will be present in solution than for a similar ester. Unless the concentrations of the base form (the species of the drug that actually diffuses into the axonal membrane) are calculated, the amides will appear to be more potent.

This difference in potency between esters and amides has been noted before. In his original work on the amide drugs, Lofgren (1948) related the potency of a large series of lignocaine analogues to lipid solubility. Although there was a very good correlation, procaine did not fit the relationship. Similarly, Courtney (1980) found a good correlation between the lipid solubility of a series of amide drugs and their frequency-dependent blocking characteristics, but neither amethocaine or procaine fitted this relationship. In both studies the points for the ester drugs lay "below and to the left" of the amide regression line, just as they do in figure 4.

Lofgren (1948) also pointed out that the slope of the regression between potency and lipid solubility was less than unity (0.88 in figure 4). He concluded that the Meyer–Overton rule does not apply to local anaesthetics so that, while lipid solubility is important, it is not the only factor affecting their potency. He considered that, if two agents had the same lipid solubility but one was more potent than the other, then it had a more "specific" action. Possibly, there is something about the ester structure that allows a closer interaction with the local anaesthetic receptor than an amide.

Although the local anaesthetic receptor has yet to be clearly located, let alone characterized, much is known about the structure–activity relationships of local anaesthetic drugs and two possible explanations for the greater potency of the esters have been put forward (Courtney and Strichartz, 1986). First, the amide bond is much "bulkier" and may physically restrict the access of the drug molecule to its binding site. Second, the o-methyl groups present on the aromatic ring of lignocaine and its analogues (fig. 1) may also interfere with binding to a receptor by causing the adjacent carbonyl oxygen to project away from the molecule. Procainamide contains an amide linkage, but no o-methyl groups (fig. 1). Since it fits the regression for the amides very closely (fig. 4), this would suggest that it is indeed the "bulkiness" of the amide bond which is responsible for the lower potency of this group of agents.

The results for procainamide are interesting in another way. On the plot of ED_{50}[base] against *C'*log *P* (fig. 4), its point lies very close to that for W36017. However, a marked difference was noted between them in the rate of development of differential nerve blockade. This is illustrated in figure 5, which shows the onset of A and C fibre blockade with approximately equipotent concentrations of the two drugs. The explanation for this would again seem to be related to pK_a. At physiological pH, approximately 50% of W36017 would be in the un-ionized, lipid soluble base form, but only 1% of procainamide. This would allow more rapid penetration of W36017 through the lipid diffusion barriers around A fibres. After the earlier study of procaine analogues, we felt that the rate of development of differential nerve blockade was not related to pK_a, but rather to lipid solubility. The compounds examined had similar dissociation constants, but very different lipid solubilities and the effect of the latter probably obscured any effect of pK_a. The rate of penetration of a drug through lipid membranes will depend on its pK_a, as well as its lipid solubility, since the former will affect the amount present in the lipid permeant form.

The above analysis is very dependent on the use of *C'*log *P* as an index of lipid solubility. Ideally, potencies should be related to measured partition coefficients, but this would require figures that had been obtained under constant laboratory conditions. Such data are not available for all the compounds studied here. When the figures that are available are compared, considerable variation is apparent, not just in absolute terms but, occasionally, even in relative values. This is because different groups of workers have examined only a few compounds and have used different analytical methods and experimental conditions. There is a great need for definitive measurements, but as a substitute the calculation of *C'*log *P* is relatively straightforward and the method is internally self-consistent, so that using the figures to compare compounds should be a valid exercise. Perhaps the most extensive data on partition coefficients were obtained by Lofgren (1948) and, as mentioned above, his results gave the same relative difference in potency between procaine and the amides as is shown in figure 4.

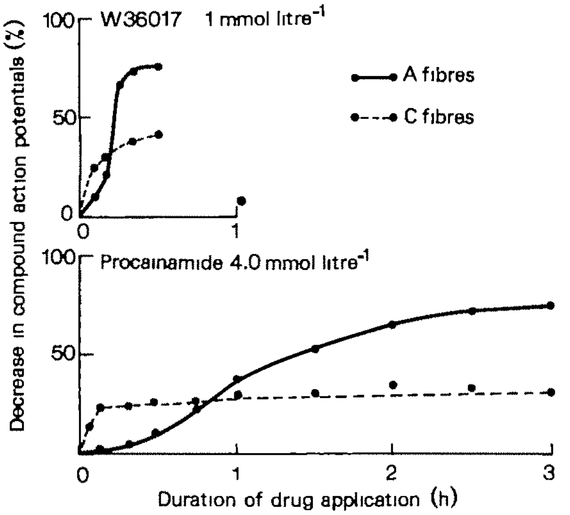


FIG. 5. Percent decreases with time in the compound action potentials for A and C fibres when exposed to W36017 1.0 mmol litre^{-1} and procainamide 4.0 mmol litre^{-1}.

CONCLUSION

This study has examined the differential nerve blocking activity of three amide-linked local anaesthetics. The results have been compared with those obtained in a similar study of a series of ester-linked agents and procainamide. There is a major difference between the clinical situation and the conditions under which these studies were performed, but the implication of the results is that C fibres would be blocked differentially by an agent of low lipid solubility and high pK_a. A compound with these properties might produce blockade of C fibres relatively quickly, but *in vivo* would be removed by the circulation before it could penetrate the greater diffusion barriers around A fibres.

If it is assumed that pain is mediated by C fibres and motor function by A fibres, the type of blockade outlined above would produce analgesia without motor paralysis—a desirable aim in several clinical situations. This simple definition of fibre function is almost certainly an over-simplification, but it is a useful working hypothesis. Using cocaine, an agent that has a relatively low lipid solubility and a high pK_a, Bahar and Rosen (1973) were able to manipulate its concentration until they produced analgesia without motor paralysis after subarachnoid injection in rats.

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ELAPID SNAKE BITE

D. K. PAWAR AND H. SINGH

SUMMARY

Four patients were admitted with respiratory muscle paralysis following an elapid snake bite. Two were treated with antivenine, repeated doses of neostigmine and artificial ventilation; the other two with artificial ventilation only. There was no clinically significant difference in recovery. It is suggested that one should avoid the use of antivenine and neostigmine in the management of elapid snake bite once muscle paralysis has become established.

More than 30000 people die each year as the result of a snake bite, the vast majority in India and South East Asia (Green, 1983). In the Indian subcontinent most of the deaths are ascribed to bites from snakes of the Elapidae family, although bites from snakes of the Viperinae family are also common (Wig and Vaish, 1960). In Elapid bite neurotoxins are believed to cause muscle paralysis and death.

The appreciation of the curare-like neuromuscular blocking action of snake venom dates back to the work of Fayrer (1872), and Kellaway, Chenny and William (1932). The resemblance to a non-depolarizing blockade, producing muscle paralysis, led to the belief that artificial respiration should form an important part of therapy. This has been shown to be so in dogs (Gode, Tandon and Bhide, 1968) and man (Campbell, 1964; Mehta, Kelker and Parikh, 1968; Bhatnagar, 1969; Casale and Patel, 1974; Naphade and Shetti, 1977; Mishra et al., 1978). However, the actual role of artificial respiration does not appear to have been studied in depth. Elapid bites have been managed using antivenine, neostigmine, antihistamines, steroids and antibiotics. After the onset of the symptoms of muscle weakness, the role of neostigmine and antivenine is debateable (Green, 1983); however, no previous workers have withheld these in favour of artificial respiration alone.

We present four cases of the successful management, using two different regimens, of elapid bite in patients in respiratory failure following muscle paralysis who were admitted to our Intensive Care Unit.

Patient No. 1

A 58-year-old male attended hospital, 3 h after being bitten by a krait, with drowsiness, loss of vision, generalized weakness of muscles, and dyspnoea which gradually progressed to unconsciousness and respiratory arrest in the Emergency Department. He was treated with polyvalent antivenine 50 ml, neostigmine 2.5 mg with atropine 1.0 mg i.v., and intermittent positive pressure ventilation (IPPV) was instituted. Antivenine 20 ml i.v. was repeated after 4 h and neostigmine (plus atropine) 2-hourly for 24 h. He had regained consciousness by 4 h, started breathing spontaneously by 5 h and was discharged after 24 h.

Patient No. 2

A 15-year-old male was bitten by a cobra while sleeping on the floor. He became drowsy 4 h after the bite. On the way to hospital, muscle weakness developed, and he became dyspnoeic, cyanotic and unconscious. On arrival at the hospital (approximately 9 h after the bite) he had a cardiorespiratory arrest. He was resuscitated and artificial ventilation was instituted. Polyvalent antivenine 40 ml i.v. was given, and neostigmine 2.5 mg with atropine 1.0 mg i.v. administered 2-hourly for 48 h. Antibiotics and antihistaminics were administered because of swelling at the bite

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area. On his admission to the ICU, his limbs were flaccid, deep tendon reflexes were absent, his plantar reflex was flexor, and there was absence of pupillary, corneal, oculo-cephalic and cilliospinal reflexes. The cold caloric test was negative. By 24 h his reflexes were normal; consciousness was regained and he had started breathing spontaneously by 48 h. Artificial ventilation was discontinued by 72 h and he was discharged by 108 h.

Patient No. 3

A 60-year-old male was brought to hospital immediately after a cobra bite. He was asymptomatic, but while under observation became drowsy, and developed weakness of the muscles, ptosis and dyspnoea. A dose of neostigmine 1.0 mg with atropine 0.5 mg was administered in the Casualty Department when he became dyspnoeic. This progressed to a respiratory arrest which was managed using mechanical ventilation. Antibiotics and antihistaminics were given because of local swelling. He regained consciousness after 10 h, breathed spontaneously by 14 h, and was discharged after 48 h.

Patient No. 4

Two brothers were bitten by a krait while sleeping on the floor. They developed muscle weakness, difficulty in breathing and became drowsy after about 4 h. On their way to the hospital one brother died. The other, a 25-year-old male, was unconscious with shallow respiration on admission 9 h after the bite. A single dose of neostigmine 1.0 mg (plus atropine 0.5 mg) was administered in casualty. A respiratory arrest occurred, and IPPV was commenced using a Bird respirator. He regained consciousness by 4 h, started breathing spontaneously by 24 h, was weaned from the ventilator by 48 h, and was discharged (with mild ptosis) by 72 h.

In all patients ECG was monitored continuously and heart rate, arterial pressure, urine output, respiratory rate, tidal volume and blood-gas tensions were measured hourly. Temperature was measured. Routine haematological and biochemical screening was undertaken; all values were within normal limits in all patients.

DISCUSSION

The first two patients were treated with antivenine, neostigmine and artificial respiration. It is generally agreed that use of antivenine is associated with serum reaction or anaphylaxis. In 61 administrations of antivenine, Campbell (1969) observed severe side effects in 40% of which 8% were serious and life-threatening. In addition, the use of antivenine always carries the danger of sensitizing the patient to horse serum. Experiences with antivenine in elapid bite induce scepticism as the muscle paralysis does not improve, frequently continues to progress and many even develop after the administration of the antivenine (Campbell and Young, 1961; Bhatnagar 1969; and Mishra et al., 1978).

When given in repeated doses after antivenine, neostigmine was thought to expedite recovery (Santosh and Usagaonkar, 1968; Bannerjee et al., 1972; Pandey, Singh and Sinna, 1979). Although there is experimental evidence from nerve-muscle preparations that neostigmine can reverse the paralysis produced by pure cobra neurotoxin (Lee, Chang and Chen, 1972) whether it can reverse the paralysis produced by the crude venom is not clear. Neostigmine is less effective, or ineffective, in antagonizing the paralytic effects of elapid bite partly because of the irreversibility of the action of post-synaptic toxins, by uneven blockade of synapses and partly by the actions of other constituents of the venom such as phospholipase A and cardiotoxin which inhibit the muscle directly (Chang, 1979).

Fayrer (1872) has observed that artificial respiration abolished the cyanosis and convulsions produced by cobra venom. Gode, Tandon and Bhide (1968) observed, in envenomated dogs, that artificial respiration reduced mortality. In man, Mehta, Kelker and Parikh (1968), Bhatnagar (1969), Casale and Patel (1974), Naphade and Shetti (1977), and Mishra and colleagues (1978), have reported the successful management of elapid bite with artificial respiration along with antivenine and neostigmine. Our later two patients were managed using artificial respiration alone and, despite the differences in their management, there was no clinically significant differences in the recovery of all four patients.

In conclusion, artificial respiration alone suffices in the management of elapid snake bite, provided there is monitoring of vital functions and good nursing care. After the onset of muscle paralysis, the administration of antivenine and neostigmine does not appear to alter the clinical course and outcome. Because of the high incidence of complications associated with antivenine and neostigmine and their doubtful efficacy in reversing muscle paralysis, we suggest that they be avoided in the management of elapid snake bite.

Note added in proof: Subsequent to the submission of this article, the first author has managed six more victims of elapid snake bite in respiratory failure following muscle paralysis, using artificial respiration alone. All six patients recovered from muscle paralysis by 72 h.

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CORRESPONDENCE

THE STOKER REPORT

Sir,—Many of your readers will now be aware of the Stoker Report which criticizes the fundamental concept of the Clinical Research Centre and recommends that either it be merged physically with the Royal Postgraduate Medical School or it should not be maintained as such at Northwick Park Hospital.

Anaesthesia is a relatively small discipline at the Clinical Research Centre, amounting to only 4% of the staff. Nevertheless, it would be a serious matter for our specialty if we were to lose either or both of the Hammersmith or Northwick Park academic departments. This is not the occasion to challenge the report, but to state the facts in relation to our own specialty.

The report is a political analysis, and assessment of scientific merit was outside the remit of the committee. An important and, indeed, the major criticism of the Clinical Research Centre concerned the relationship between the NHS staff of Northwick Park Hospital and the MRC staff of the Clinical Research Centre. This was set out in section 2.10:

"We conclude that there is a growing divergence of the two populations of clinical staff on site. The symbiotic relationship of MRC and NHS staff which we understand to have been a real feature of the early days seems largely to have disappeared, although there are, of course, outstanding exceptions."

We are not to know who are the "outstanding exceptions" but it needs to be put on record that the Clinical and CRC Divisions of Anaesthesia have enjoyed the very closest relationships for the past 16 years. The consultant anaesthetists of Northwick Park Hospital, in their role as honorary members of the CRC scientific staff, have played a crucial part in the initiation and prosecution of projects. We would have been greatly hampered without their active participation. Of the 600 papers published during the 16 years of the CRC Division of Anaesthesia, 105 include in their authorship one or more of our NHS consultants. In addition, junior hospital staff in the NHS Division of Anaesthesia have played a major role and feature amongst the authors of 40 papers. I could not have wished for stronger support from our NHS colleagues. The two Divisions of Anaesthesia have, in my view, borne out to the letter the original concept of Northwick Park as a partnership of the Clinical Research Centre and a District General Hospital.

J. F. Nunn
London

HUNTINGTON'S CHOREA: MIDAZOLAM, A SUITABLE INDUCTION AGENT?

Sir,—Recent developments in short acting i.v. anaesthetic agents have produced a new approach to anaesthesia in Huntington's chorea. Johnson and Heggie (1985) used alfentanil and Althesin for induction, atracurium for neuromuscular blockade and alfentanil, Althesin, nitrous oxide and oxygen for maintainance. These alleviated the prolonged clinical responses to thiopentone (Davies, 1966; Blanloeil, Bigot and Dixneuf, 1982) and suxamethonium (Gualandi and Bonfanti, 1968; Whittaker, 1980).

The withdrawal of Althesin from the market highlights again the problem of induction in patients with Huntington's chorea since, although volatile agents like halothane (Lamont, 1979) and either (Davies, 1966) have been used for this purpose, the induction of anaesthesia using a face mask is unpopular with many patients. The recently introduced short-acting benzodiazepine, midazolam, may be a useful alternative.

A 54-year-old Caucasian weighing 64 kg, with a history of Huntington's chorea, was admitted for examination, extraction and conservative work on his teeth. The patient had been diagnosed as suffering from Huntington's chorea 1 year previously and had a history of increasing forgetfulness. His parents had died when he was a child. His speech was slow and dysphasic. He had some involuntary movements of the arms and an ataxic gait. He was receiving tetrabenazene 25 mg three times a day. This was continued up to the time of the operation.

The night before the operation, diazepam 5 mg was given orally as a sedative. He slept well. The following morning he was given another 5 mg of diazepam as premedication and one tablet of tetrabenazene.

When the patient arrived in the anaesthetic room he appeared to be asleep, but answered questions drowsily when spoken to. His systolic arterial pressure (Dinamap) was 100 mm Hg and heart rate 46 beat min^{-1}. Preoxygenation was carried out, an i.v. cannula was inserted to a vein in his left hand and fentanyl 0.05 mg given. Heart rate decreased to 39 beat min^{-1} and atropine 0.6 mg was given. Anaesthesia was induced with midazolam 5 mg i.v. given slowly over about 2 min—until the eye-lash reflex was lost. At this time alcuronium 15 mg was injected and nitrous oxide and oxygen supplemented with halothane substituted for 100% oxygen. Gradually, ventilation was controlled by hand. A nasotracheal tube was passed and a throat pack inserted. Ventilation was controlled (Manley ventilator) with nitrous oxide, oxygen and halothane. The operation lasted about 2 h and was uneventful: systolic arterial pressure was between 100 and 123 mm Hg and heart rate 77–85 beat min^{-1}. He did not need any supplements of alcuronium. At the end of the procedure he received neostigmine and atropine for reversal of the paralysis and following this he started to breathe. The throat pack was removed, the nasopharynx was evacuated, and the trachea was extubated with the patient on his side with a slight head-down tilt.

The patient recovered consciousness within 10 min of the end of the operation, and recovery was uneventful other than occasional, brief tonic spasms and choreiform movements.

When questioned next day in the ward, he was amnesic for all events of the previous day up to the time of being awake in the ward in the evening.

In this patient bradycardia was noted following a small dose of fentanyl—as reported for patients studied by Grell, Koons and Denson (1970). This was reversed with atropine 0.6 mg. Subsequently, induction was carried out with midazolam (Allonen, Ziegler and Klotz, 1981), with profound amnesic effects. Induction took about 2 min. The small dose (5 mg) needed would have been attributable to the pathological changes in brain, and potentiation by the premedication and tetrabenazene. The action of midazolam, similar to that of diazepam, would have facilitated the depleted GABA action. Farina and Rauscher (1977) obtained smooth induction with fentanyl and diazepam. However, midazolam would be a better alternative because its action is shorter, it produces profound amnesia and it is water soluble, with a decreased incidence of thombophlebitis (Dundee, 1975).

Halothane was used as the volatile agent. Supplements of volatile agents (trichloroethylene, ether and halothane) have been used previously. In patients who received trichloroethylene, generalized tonic spasms have been seen after operation (Davies, 1966). With ether (Davies, 1966) and halothane (Farina and Rauscher, 1977; Lamont, 1979; Wells, 1979) the recovery was smooth. However, unlike the previous experiences with halothane, our patient initially developed halothane-induced postoperative shivering which precipitated tonic spasms. Thus from this experience it may be advisable to avoid halothane in these patients if an alternative is available.

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ANALYSIS OF COSTS OF ANAESTHETIC BREATHING SYSTEMS

Sir,—Few studies of the economy of the various anaesthetic breathing systems have been performed (Edsall, 1981). As the semi-open systems are now used widely, we have compared the expense of using the circle system and these systems. The calculations were performed with various fresh-gas flows and halothane concentrations, and with various regimens of utilization of the absorber. Other expenses, such as salaries, i.v. anaesthetics and maintenance of equipment are assumed to be independent of the choice of anaesthetic breathing system.

If the carbon dioxide absorber is used for a fixed period of time, the cost of soda-lime depends upon the duration of the anaesthetic procedure. If, however the absorber is changed after each operation, the cost per unit time will depend on the duration of the anaesthetic. The present calculations were based on the latter assumption. In circle systems a smaller fresh-gas flow is usually used, compared with the semi-open systems. If the absorber is changed before each anaesthetic, the circle system will be the cheapest system in prolonged operations, and the semi-open systems will be the cheapest for short operations. The duration of anaesthesia, at which the expenses are equal, is defined as the iso-cost point. This can be expressed in the formula:

$$Y \cdot B \cdot C = (Y \cdot X \cdot B) + A$$

where Y = iso-cost point; X = fresh-gas flow in the circle system; A = cost of soda-lime per anaesthesia; B = cost per litre of anaesthetic gas mixture; C = fresh-gas flow in the semi-open system.

The formula can be changed to:

$$Y = \frac{A}{B\,(C-X)}$$

This is the formula of the "iso-cost curve", which illustrates the variations of the iso-cost point with different fresh-gas flows in the circle system. The curves will be independent of changes in prices or currencies, provided that the changes are proportionate.

Some examples of iso-cost curves are illustrated. In figure 1, from the curve, the iso-cost point can be found using various flows in the circle system. For example, if a fresh-gas flow of 5 litre min^{-1} is used in the circle system (which is common practice), it is cheaper to use a semi-open system with fresh-gas flow of 10 litre min^{-1} for procedures lasting less than 50 min. If lower fresh-gas flows are used, for example 3 litre min^{-1} in the circle system and 6 litre min^{-1} in the semi-open system, then the iso-cost point is 83 min.

The calculations in figure 2 are made for various halothane concentrations. When increasing halothane concentrations are used, the expense of the anaesthetic gas mixture increases simultaneously. For example, when a fresh-gas flow at 3 litre min^{-1} in the circle system is used with 0.5% halothane, then the iso-cost point is 119 min. If 2% halothane is used, then the iso-cost point will be 53 min.

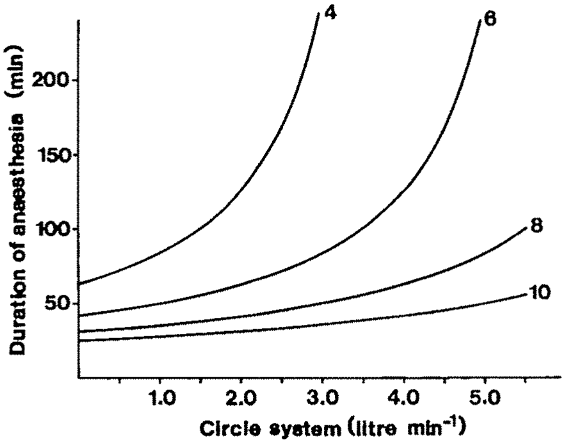

FIG. 1. Iso-cost curves. Fresh-gas flow to semi-open system: 4, 6, 8, 10 litre min^{-1}. Nitrous oxide in oxygen 2:1; 1% halothane; soda-lime 600 g.

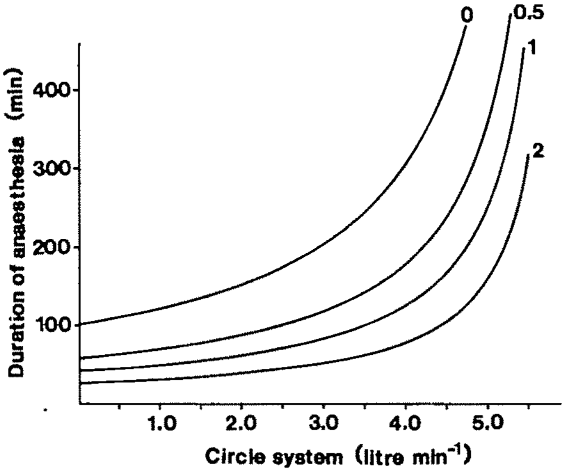

FIG. 2. Iso-cost curves. Fresh-gas flow to semi-open system: 6 litre min^{-1}. Nitrous oxide in oxygen 2:1; halothane concentrations 0, 0.5, 1, 2%; soda-lime 600 g.

Figure 3 demonstrates that, with repetitive use of the soda-lime, expenses decrease in the circle system, which will be the cheapest in use for operations exceeding 17 min, if the absorbent is re-used for five patients and the fresh-gas flow to the circle system is 3 litre min^{-1}.

The present calculations show that, in procedures lasting less than about 1 h, the semi-open system are more economical than the circle system used with traditional gas flows (about 4 litre min^{-1}).

The iso-cost curves are used to illustrate graphically the economic consequences of varying halothane concentrations, gas flows and absorber utilization. In previous studies concerning economy, some authors have considered the cost of soda-lime (Bailey, 1978; Simpson, 1978; Edsall, 1981), while others have not (Briscoe, 1970; Nunn, 1979; Virtue, 1979).

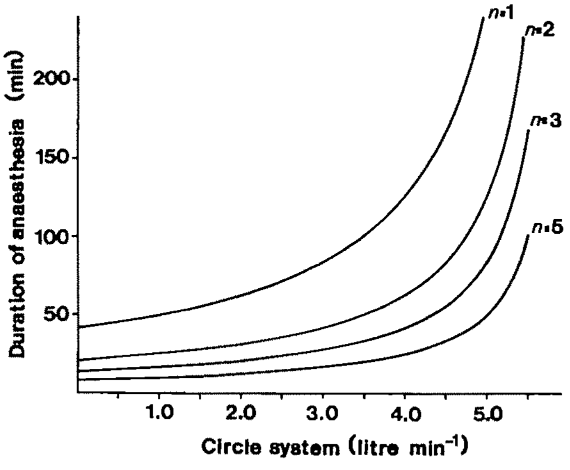

FIG. 3. Iso-cost curves. Fresh-gas flow to semi-open system: 6 litre min^{-1}. Nitrous oxide in oxygen 2:1; 1% halothane. Soda-lime 600 g. (Used for 1, 2, 3 and 5 patients (n = number of patients).)

The cost of soda-lime is important, when the economy is illustrated by means of the iso-cost curves.

The iso-cost curves appear very useful for training and are easily computerized from the formula during other conditions, such as change in prices.

Previous publications show a tendency to use fresh-gas flows in circle systems, which are close to the alveolar ventilation in adult patients (5–6 litre min^{-1}). By the use of a Mapleson D system with identical fresh-gas flow, this will always be the cheapest in use and protects the patient against accidental hypocarbia. The use of circle systems for shorter lasting operations thus cannot be justified from an economic point of view.

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SINUS ARREST AFTER ALFENTANIL

Sir,—We wish to report two cases of sinus arrest during intubation following administration of alfentanil 30 $\mu g\ kg^{-1}$.

Laryngoscopy and tracheal intubation have been shown to produce a marked increase in heart rate (Millar and Dally, 1970). Pretreatment with alfentanil 30 $\mu g\ kg^{-1}$ has been shown not only to abolish this tachycardia, but also to produce a relative bradycardia significantly lower than control values 4 min after the administration of the alfentanil (Black, Kay and Healy, 1984). This suggests that the alfentanil may have attained a higher level of activity at this time, indicating a more appropriate moment to intubate.

We had intended to study two groups of 20 patients. Patients were premedicated orally with temazepam 10–20 mg. ECG monitoring was commenced on arrival in the anaesthetic room. Anaesthesia was induced with alfentanil 30 $\mu g\ kg^{-1}$ given over 20 s, followed after 1 min by thiopentone 4 $mg\ kg^{-1}$ and suxamethonium 1 $mg\ kg^{-1}$. The patient's lungs were ventilated by hand with 50% nitrous oxide in oxygen. Laryngeal spray (lignocaine 3 $mg\ kg^{-1}$) and intubation were performed in group 1 after 30 s and in group 2 after 2 min.

In group 1 the lowest mean heart rate for the group was 63 beat min^{-1} and occurred at intubation; the lowest individual recorded heart rate was 42 beat min^{-1}. The study of group 2 was abandoned after six patients had been studied because two patients suffered sinus arrest at the onset of laryngeal spraying. The durations of sinus arrest were 10 and 12 s. In both patients spontaneous reversion to nodal and then sinus rhythm occurred. A third patient developed a bradycardia of 37 beat min^{-1}. All patients recovered uneventfully.

It has been shown in the paralysed, artificially ventilated animal model that stimulation of either the laryngeal or tracheobroncial mucosae produces increases in both cervical sympathetic and vagal outflow (Tomori and Widdicombe, 1969). We suggest that similar changes occur in man, and that high-dose opioid pretreatment may attenuate or completely abolish the sympathetic element of this response which allows unopposed vagal activity to produce bradycardia and sinus arrest. Our results suggest that, in the case of alfentanil, this effect is most pronounced if intubation is undertaken 4 min after the administration of the opioid.

There may be a number of reasons for the high incidence of sinus arrest in our patients: First, the use of a potent opioid with a rapid onset of action may result in a greater degree of attenuation of the sympathetic response at the time of laryngeal stimulation. Second, we did not use a neuromuscular blocker with ganglion stimulating properties, such as pancuronium. Third, the presence of increased acetylcholine concentrations as a result of the breakdown of suxamethonium may accentuate the vagal response.

Fortunately, our patients were free from cardiovascular disease and suffered no sequelae. The outcome in patients with cardiac disease might be less favourable.

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ACUTE (TYPE 1) HYPERSENSITIVITY TO I.V. DIAZEMULS

Sir,—Side effects from diazepam formulations are well documented. Pain on injection and thrombophlebitis are the two main disadvantages (Jensen, Huttel and Schou Olesen, 1981). The advent of using fat emulsion as a carrier for diazepam (Diazemuls, Kabi Vitrum, Ltd, London) has reportedly largely done away with these problems (Selander, Curelaru and Stefansson, 1981; Bullimore, 1982; von Dardel et al., 1983) without reducing the efficacy of the drug.

Type 1 hypersensitivity to Diazemuls is unrecorded in the literature, although acute anaphylaxis to Intralipid has been documented (Kamath, Berry and Cummins, 1981). We report a case in which there was a Type 1 hypersensitivity reaction to an i.v. injection of Diazemuls.

A 48-year-old epileptic man presented to our Accident and Emergency Department with a history of a fit, witnessed by his wife. This was probably precipitated by alcohol. He had not received any anti-epileptic treatment for 4 years and had remained fit-free during this time. Whilst being examined he had a focal motor seizure which was controlled by Diazemuls 10 mg i.v. The patient immediately became dyspnoeic and cyanosed with widespread bronchospasm. He also developed an urticarial rash. He had a tachycardia of 120 beat min^{-1}, but his arterial pressure was not recorded at this time. He was resuscitated with oxygen, aminophylline and hydrocortisone, and his bronchospasm resolved over the next 30 min. Further fits were controlled with i.v. chlormethiazole.

As there was no history of asthma, bronchitis or subsequent evidence of foreign body inhalation, his sudden deterioration was attributed to Diazemuls.

Skin pin-prick tests later supported this theory. A local urticarial reaction was produced by Diazemuls, but not by diazepam or 10% Intralipid. Similar pin-prick tests were carried out on 10 control subjects, five of whom had been recently exposed to i.v. Diazemuls and five who had no history of exposure to i.v. sedation or intralipid. In all cases the results were negative. There was no recorded evidence that our patient had been previously exposed to Diazemuls.

We conclude that our patient had an acute (Type 1) hypersensitivity reaction to Diazemuls, and suggest that the reaction was to the lipid vehicle of the particular preparation.

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BOOK REVIEWS

Postoperative Pain: Understanding its Nature and How to Treat It. By Jane Hosking and Edward Welchew. Published by Faber and Faber Ltd. Pp. 175; indexed; illustrated. Price £4.95.

This book is intended to help nurses and other non-medical staff understand and appreciate the problems associated with pain following surgical procedures. The psychology, anatomy and physiology of pain are discussed adequately, and the difficulties associated with the assessment of pain described. The importance of preparing the patient in advance for the pain and other discomforts associated with the postoperative period is emphasized, and the nurse's role in the management of acute pain is reviewed. There is an adequate description of the pharmacology of analgesic drugs, and of methods of administration. While it is quite appropriate to describe in detail methods of administration which improve upon i.m. injection, the fact remains that this will almost certainly continue to be the method by which postoperative analgesia is administered to the majority of patients for many years. It is, therefore, unfortunate that i.m. injection is dismissed rather than practical advice being offered in an attempt to optimize the nurse's use of this route.

There is considerable variation in the depth of the discussion in the book; anatomy and physiology are described at a fairly simple level, while psychological aspects are discussed very fully; for example: "empathy is the power of projecting one's personality into the object of contemplation so that it can be fully understood"! There are a number of case histories and examples of nursing assessment sheets. In addition, guidance as to the conduct of analgesic trials is provided.

It is the reviewer's experience that the majority of nurses receive very little tuition in the management of pain, and that much of what they are taught is inaccurate. This book must, therefore, be recommended for its attempt to educate nurses and other non-medical hospital personnel in the importance of appreciating the pain experienced by patients following surgery, the complications which pain itself can produce, and the provision of adequate treatment. There should be a copy on every surgical ward.

Alan R. Aitkenhead

Spinal Opioids and the Relief of Pain. Edited by J. M. Besson and Y. Lazorthes. Published by I.N.S.E.R.M., Paris. Pp. 518; illustrated. Price 187.25 FFr.

This book is a collection of papers presented at a multidisciplinary international symposium in Toulouse in 1984. It is in two parts. The first deals with the fundamental scientific aspects and the second with the clinical treatment of pain. At the end of the book there is also a short section of communications, The book is published in France; eight of the articles are in French with a summary in English and 16 are in English. The communication section contains only short summaries, which are mostly in French.

The articles in this book are of a high quality and although some are extremely specialized dealing with, for example, the biochemistry of the opioids in great detail, there is enough information of clinical interest and relevance to make it well worthwhile obtaining this book for any departmental or university library. Some of the chapters give insight to future directions in the pharmacology of analgesics, both in the development of new opioids and also in novel approaches such as interfering with the metabolism of endogenous opioids.

In the part of the book dealing with clinical applications, all the articles concern, in one way or another, spinal opioids and range from general articles such as the one by Philip Bromage reviewing the whole subject, to more specialized articles looking at the treatment of cancer pain by intraspinal opioids, or at methods of delivery.

Overall this is a fascinating book, not only for its excellent contents, but also because of the concept of bringing together basic scientists and clinicians.

W. A. MacRae

Muscle Relaxants. Basic and Clinical Aspects. Edited by R. L. Katz. Published by Grune and Stratton. Pp. 305; indexed; illustrated.

With the advent of the two new non-depolarizing muscle relaxants, atracurium and vecuronium, it is not surprising that there has been a resurgence of interest in the neuromuscular junction. This interest has encompassed not only the pharmacology of all the currently used neuromuscular blocking agents, but also the recent advances in our understanding of the physiology of neuromuscular transmission. Topics such as the monitoring of neuromuscular function and the problems encountered when muscle relaxants are used in patients suffering from a variety of pathological states have been resurrected recently. All these subjects are of great interest and practical concern to the anaesthetist who is researching in some aspect of neuromuscular function and, indeed, to those studying for the Final part of the Fellowship examination. Thus there is undoubtedly a place for a monograph such as this in the research worker's, although perhaps not the clinician's, library. The empty space may well have been filled already, however, by a very similar publication, released only last year: *Anaesthesiology Clinics: Neuromuscular Blockade* (ed. J. Norman. London: W. B. Saunders Co.). These two monographs are so similar that many of the international authorities on the neuromuscular junction have contributed to both, although in some instances they have exchanged topics, as if playing a game of neuromuscular "musical chairs".

In addition, before purchasing this book, it should be realized that it is obtainable in an alternative form—as two volumes of the American Journal, *Seminars in Anesthesia*, which can be obtained by post from the same publishers at a similar price. Many doyens in this field may have already availed themselves of this facility and the more fortunate may well have received one volume free of charge!

If neither of these publications has been acquired already, however, this paperback book is a useful compendium for those interested in neuromuscular function. It is easy to read, with a pleasant typeface and plenty of diagrams. It slips into the pocket, a man's pocket anyway, and is well indexed.

It does have a few advantages over its predecessors, in that it covers certain additional, topical subjects. There is, for example, a chapter by Rosenberg on the use of muscle relaxants in patients with neuromuscular disorders, a subject on which even more detailed reappraisal would be valuable. Viby-Mogensen contributes a chapter on the interaction of "other drugs" with muscle relaxants. This is a difficult subject about which to write; it is hard to classify and the author has attempted it in tabular form for easy reference.

At the end of the book, a new "appetizer" is discussed: namely the pharmacology of 4-aminopyridine, a substance which not only reverses residual neuromuscular blockade, but possibly reverses sleep and analgesia too. Derivatives of this substance may well be the reversal agents of the 21st century, and offer an exciting field of further research.

As with any book written by several contributors, there is more repetition of information than is necessary, if the reader does not know the disadvantages of using suxamethonium after reading this monograph, then he never will. It is indeed unfortunate that the book has no preface, for it is not clear for whom it is intended. I am sure however that, for any anaesthetist interested in neuromuscular blockade, it would be a useful little adjunct to their library.

J. M. Hunter

International Anesthesiology Clinics. Anaphylactoid Reactions in Anesthesia. Edited by D. J. Sage. Published by Little, Brown & Co., Boston. Pp. 193; indexed.

This book is devoted entirely to drug-induced anaphylactoid reactions of relevance to anaesthesia and, as such, is an expansion of what has, until now, been covered in one or two chapters in the larger textbooks. Although there is a wealth of useful information about the incidence and immune mechanisms involved in reactions to specific drugs, the way in which the book has been written has inevitably resulted in considerable repetition—particularly in the areas of diagnosis and treatment. I wonder how detailed was the editor's brief to each author and, indeed, how much liaison took place between them. The book is extensively referenced at the end of each chapter and contains a comprehensive index.

The first chapter describes the clinical presentation of anaphylactoid reactions, giving a comprehensive account of the symptoms, incidence, predisposing factors and outlining the mechanisms involved in individual groups of drugs. I found Chapter 2, specifically devoted to the mechanisms involved, rather superficial in a book totally devoted to this subject. There is little mention of antibody types or their significance in the differential diagnosis of adverse reactions occurring on multiple drug exposure— a common problem in anaesthesia. The contents of chapter 1 are often reiterated and methohexitone, for some reason, is singled out for individual discussion. There is a short section on treatment which is reproduced at greater length later in the book. The third chapter deals specifically with the histamine-releasing potential of drugs—i.v. induction agents, neuromuscular blockers, etc., and the mechanisms involved, together with a short section on its prevention.

The next four chapters deal with reactions to specific groups of drugs, namely colloidal solutions, radiocontrast media, chemonucleosis using chymopapain, and protamine. Each contains a review of the agents concerned, the pathophysiology and immune mechanisms involved and the treatment. Although comprehensive, I find it difficult to see the relevance of including either radiocontrast media or chemonucleosis, when there are no chapters dealing specifically with drugs used in everyday anaesthetic practice such as i.v. induction agents, neuromuscular blocking drugs or analgesics.

For some reason, the French experience of diagnosis and management of anaphylactoid reactions has merited a separate chapter, although I cannot see why one country's experience has been singled out, or why it should be any different from North America, the U.K., Australasia, or other European countries. Their work on diagnosis and skin testing, however, is certainly of relevance, but considerably overlaps and pre-empts what appears in the next chapter specifically devoted to this.

The final chapter, while being a comprehensive study of the management and treatment of anapylactoid reactions, reiterates what has already been said repeatedly in other chapters dealing with the specific agents. While being pleased to see a whole book devoted to this increasingly important anaesthetic topic, I was disappointed at the apparent lack of facts and discussion about specific, everyday anaesthetic drugs as opposed to rather exotic agents, particularly since this is the title of the book. The special nature of the problem of drug-induced anaphylaxis, together with the essentially common methods of treating all reactions, make the book very repetitive in parts and I feel that tighter editorial control, and the inclusion of chapters of specific anaesthetic relevance, would have improved it considerably. It is a useful book but, for the clinical anaesthetist, contains little of relevance which cannot already be found in specific chapters contained in existing anaesthetic textbooks.

Peter Simpson

600 MCQs in Anaesthesia: Basic Sciences. By P. J. Simpson and N. W. Goodman. Published by Churchill Livingstone. Pp. 242.

Examinations containing multiple choice questions are hurdles which we must all cross on the way to a basic or advanced medical qualification. Early in their development it was realized that the opportunity of practising MCQs might improve results, and this textbook is another result of that specious but untested hypothesis.

The book is aimed at doctors undertaking the new Part 2 examination in basic sciences for the F.F.A.R.C.S. The authors, (one of whom is an examiner) have written or collected the questions over a number of years of organizing courses in Bristol. After an introductory chapter which tells the reader how to answer the questions—for example "you indicate your answer by filling in a 'true' or 'false' box in pencil" and..."what the examiner wants to know is whether the candidate can see the wood for the trees"—the remainder of the text consists of 10 mock papers of 60 MCQs (20 Pharmacology, 20 Physiology and 20 Physics). The question papers are followed by answers and some of the answers have one sentence explanations. The questions are not grouped in any particular category or degree of difficulty—in an attempt to mimic the actual examination.

Any criticism of this book must be directed at the approach of trainees and the profession rather than the authors. The text is not designed to be a source of knowledge (although some facts must be gained if the book is used properly), but rather to help the candidate present his knowledge to the examiners.

As long as MCQ questions exist there will be a market for books of this nature and it is perhaps a worry that candidates will spend some hours working through the questions when they would be advantaged more by studying.

Overall, the book is well produced with few errors. Although Physics is no longer a separate part of the examination, the questions are relevant to the physiology and pharmacology sections. I suppose many potential examiners and course organizers will buy or borrow a copy. I can't wait for practice essay and viva questions.

Walter S. Nimmo

Difficulties in Tracheal Intubation. Edited by I. P. Latto and M. Rosen. Published by Baillière Tindall, W. B. Saunders. Pp. 183; indexed; illustrated. Price £14.50.

The establishment and maintenance of a safe and protected airway is of paramount importance in any form of anaesthesia.

The presence of a correctly sited, cuffed tube in the trachea will satisfy this requirement. In the majority of instances a basic knowledge of anatomy coupled with meticulous technique will allow this to be accomplished without undue difficulty or hazard. Certain patients, however, present varying degrees of difficulty in intubation, and it is to this group that the authors of this text direct their attention. Their stated aim of presenting a comprehensive survey and a practical guide has been achieved with almost total success.

The anatomy of the airways is covered comprehensively and lucidly, the illustrations clear and uncluttered, although the reviewer would have wished for a more detailed description and clearer illustration of the anatomy as seen during laryngoscopy.

The chapters on pathophysiology and complications of intubation are again most comprehensive with excellent bibliography. In history, function and design of the cuff and its relation to possible side-effects and tracheal damage the author collects and collates information from wide ranging sources and is to be congratulated on his most readable and informative contribution. It is interesting that the greater proportion of the work in this section is reported by U.S. and European workers.

Chapter 5 contains an excellent account of intubation technique, but is less certain in its handling of the section on recognition of possible difficulties. The description of anatomical abnormalities would create more impact if accompanied by illustrations; more emphasis could also be placed upon the importance of the preoperative examination of the patient's profile and soft tissue structures.

The reviewer's practice comprises largely head and neck surgery for malignancy, and the cultivation of a high index of suspicion before operation has led to an increased number of potentially difficult, but fewer failed, intubations. In this regard the inclusion of a chapter of case reports and discussion is particularly valuable.

The introduction to the section on awake intubation should become the anaesthetist's 11th commandment, and this chapter and the following on the management of difficult intubation their bedside companion.

Difficult and failed intubation in obstetrics firmly emphasizes the importance of a familiar rather than a theoretically perfect approach, and includes a simple and rational plan for failed intubation.

Endotracheal intubation, familiar to an earlier generation of anaesthetists, was read with considerable interest as a refresher course, and revived many memories.

A thought provoking review on the teaching of intubation completes the book. There is in this volume much of interest and value to anaesthetists, from those learning the craft, to teachers, and experienced practitioners; it is exceptional value for money, and should—and will no doubt—find its way onto the bookshelves of many anaesthetists.

R. S. Neill

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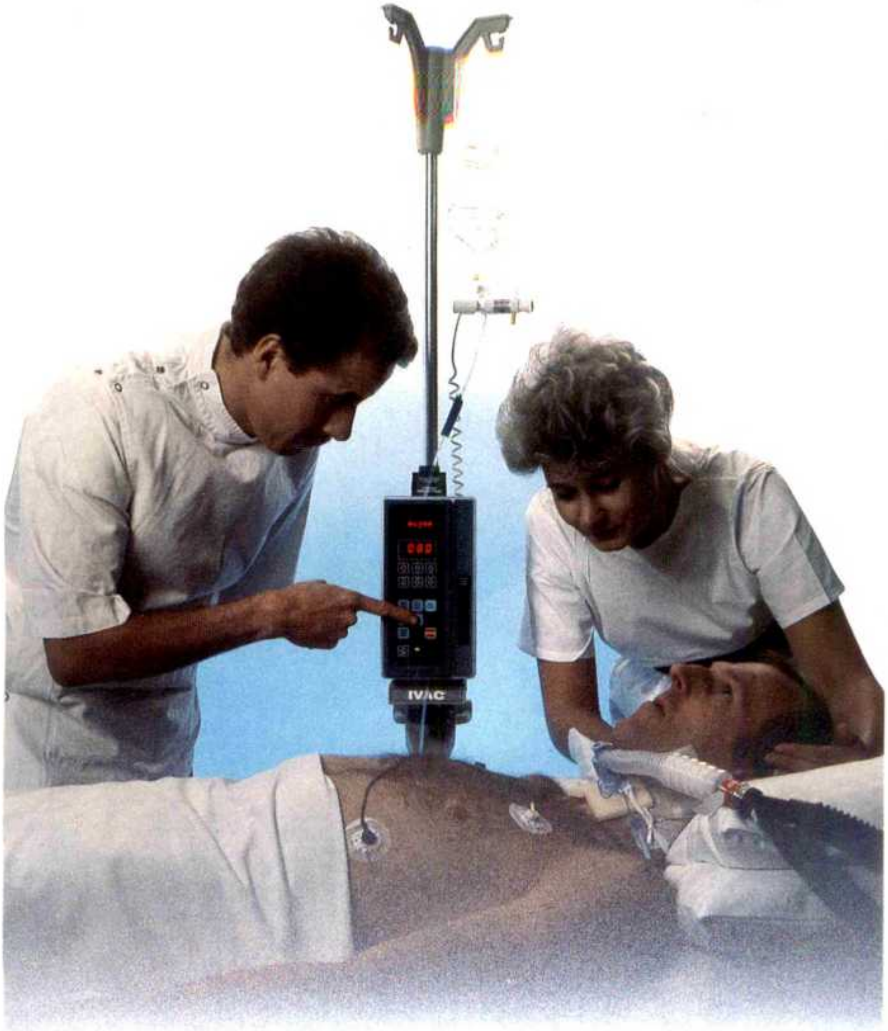

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